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# Science & Technology

## Central Eurasia: Life Sciences

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## Results of Blood Tests Among EO-2, -3, -4 Space Crews

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TRANSFUZIOLOGIYA in Russian No 7, Jul 91 pp 24-27

[Article by B. I. Legenkov, Prof. G. I. Kozinets, A. P. Andreyeva, V. V. Polyakov, V. I. Gudim, V. S. Ivanova, Ye. G. Kazanets, I. V. Ryapolova, Cosmonaut Training Center, Zvezdnyy gorodok; All-Union Hematological Science Center, USSR Ministry of Health, Moscow; UDC 616.15-057:629.78]-07]

[Text] Adaptation is one of the most important evolutionary-adaptive responses of the body to a changing environment and is a necessary requirement for his activity in new conditions of existence. All the functional systems of the body are restructured, including the adequate supply of oxygen, which is determined by the nature and level of energy processes. Indicating that restructuring are a multitude of data from the literature on changes of various erythron parameters in hypodynamia or intense muscular exertion, in exposure to adverse climate-geographic conditions, and, finally, in weightlessness and subsequent readaptation to ground conditions after a space flight.<sup>1-7,9</sup>

The hematological indices that we studied of the cosmonauts' peripheral blood, the cytomorphology of the erythrocytes, and the individual indices of erythropoiesis (the plasma level of erythropoietin, iron metabolism, hemoglobinization of erythrocytes) in the first hours after landing, as well as a comparison of results of short-duration missions (up to two to three months) and long-duration missions, made it possible to substantiate the erythrocytopenic syndrome of weightlessness.<sup>4-7</sup>

This paper presents the results of the study of several erythron indices, produced for missions of 151-366 days (1987-1989), during adaptation to weightlessness and during subsequent readaptation to ground conditions.

The yearlong space flight of the third main mission (EO-3) lasted from 21 December 1987 to 21 December 1988, with crew commander TVG, flight engineer MMKh, and the cosmonaut-researcher who came up on day 253 (30 September 1988), crew physician PVV, who was a candidate of science from the Soviet-Afghan visiting mission (EO-2/3, from 29 August to 7 September 1988) and who stayed aloft for 241 days, as part of EO-4 also, until 27 April 1989.

A distinguishing feature of the 366-day flight was that the taking of a number of blood samples and the performance of several hematological tests were done in space, aboard the Mir station, and they confirmed the blood changes we had observed earlier and the situation we had constructed.<sup>1,4</sup> Study of those materials established that on day 34 of PVV's flight, altered forms of erythrocytes were noted, with predominance of target forms (on average, 13 percent), as well as ovalocytes (up to 5 percent), spherocytes, and other forms. The target-cell erythrocytes remained throughout the flight, averaging

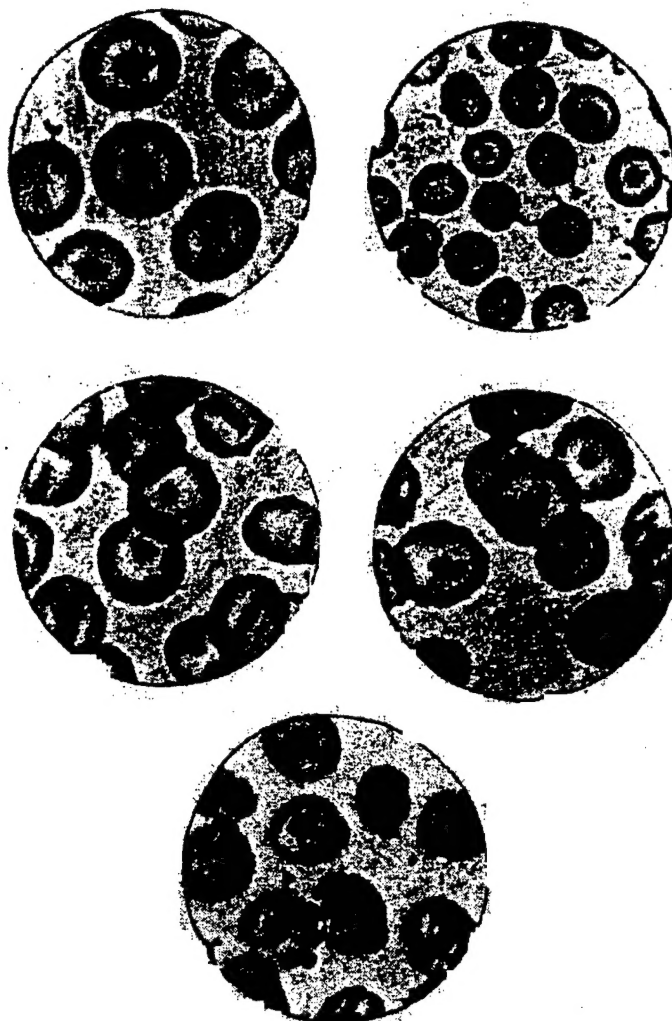
as much as 17 percent by quantity, which was evidenced by blood tests performed on days 61, 150, and 196 of the flight. In the crew commander and the flight engineer (EO-3), the number of target-cell erythrocytes in blood smears taken on days 344 and 351 increased to 31 percent (Fig. 1).

In the cosmonauts of the crew of EO-4, which was with PVV in space for 151 days, the changes in the erythrocytes showed up mainly as target-cell forms. In samples of blood taken on day 86 from the crew commander (VAA), the forms accounted for 36 percent; the forms in the blood sample taken on day 106 from the crew commander and the flight engineer (KSK) accounted for 22 percent and 26 percent, respectively. The percentage relationship between normal and target-cell forms of erythrocytes changed little by day 122 for the crew commander, but rose to 46 percent in the flight engineer.

Based on the results of the hematological studies done in the crew members of missions EO-3 and -4, as well as on the results of studies done earlier with the blood of cosmonauts who made up the crews for 10 long-duration missions from 1975 to 1986, man's stay in conditions associated with the absence of the force of gravity appears to induce a number of morphological changes in the erythrocytes. For example, the functionally active, stable, double-concave, "ground" forms of the human erythrocyte gets increasingly round in weightlessness. The hemoglobin molecules may possibly shift around in the cell, which is perceived as the presence of target-cell forms of erythrocytes, whose appearance on the ground is interpreted as pathological.<sup>8</sup> Those forms appear only in long-duration weightlessness, which points to the intimate link between the functional-physiological shaping of the erythrocyte and gravity. That point of view is also confirmed by the fact that target-cell forms and other pathological forms of erythrocytes in the cosmonauts normalize on the ground soon after landing and are rarely observed after hours or days. No long-term effects whatsoever are noted. When a cosmonaut goes back up into weightlessness, the number of target erythrocytes increases, and other blood alterations appear.

After the EO-3 crew returned from a year in space, blood samples taken nine hours and 24 hours after landing showed the number of reticulocytes to have remained low, and in TVG, they were only 30 percent of baseline (Fig. 2, left). Judging from those indices, the rate of erythropoiesis dropped during that period in both cosmonauts by an average of 60-70 percent, although no clear signs of hemolysis were identified in them. The reticulocytopenia can be regarded as a decline in the base of blood formation as a result of exposure to weightlessness.

The study of the individual indices of erythropoiesis in the postflight period in cosmonauts who have spent long periods aloft has confirmed that hypothesis. For example, the results of the erythrocyte dry mass test indicated a trend toward a decline in Hb concentration in them, which was more pronounced in PVV (to 30 pg), with subsequent



**Fig. 1. Picture of peripheral blood of cosmonauts: upper left, target-cell erythrocytes in PVV on day 34 (2 Oct 88), 12.69 percent; upper right, same cells on day 61 (28 Oct 88), 13.0 percent; middle left, target-cell erythrocytes in TVG on day 344 (30 Oct 88), 30.6 percent; middle right and bottom, target cells in MMKh on day 351 (6 Nov 88), 31.33 percent. Magnification 2500**

restoration to normal. However, in RYuV (327-day flight, 1987, EO-2), the decline in dry mass was more profound and more stable: Content of Hb dry mass dropped by 28 percent and did not normalize for nine days of observation. In the second member of the crew, who had been aloft

for 161 days (from 21 July to 29 December 1987), the same changes were observed (reticulocytopenia and hypochromia), with a consistent decline in dry mass of erythrocyte Hb by 19 percent and 18 percent, respectively, on days five and nine (see the table).

#### **Hb Dry Mass (in pg) in Erythrocytes of Cosmonauts Who Completed 327-Day Flight**

| Crew member, duration of flight, in days | Baseline data | Readaptation (p0.001) in both crew members, days |               |               |               |
|--|---------------|--|---------------|---------------|---------------|
|  |               | Day 0  | Day 1         | Day 5         | Day 9         |
| RYuV, 327                                | 34.66 +/- 0.6 | 26.1 +/- 0.41                                    | 25.58 +/- 0.4 | 25.46 +/- 0.4 | 31.92 +/- 0.5 |
| AAP, 161                                 | 33.84 +/- 0.6 | 28.62 +/- 0.6                                    | 27.68 +/- 0.4 | 27.38 +/- 0.5 | 27.72 +/- 0.5 |

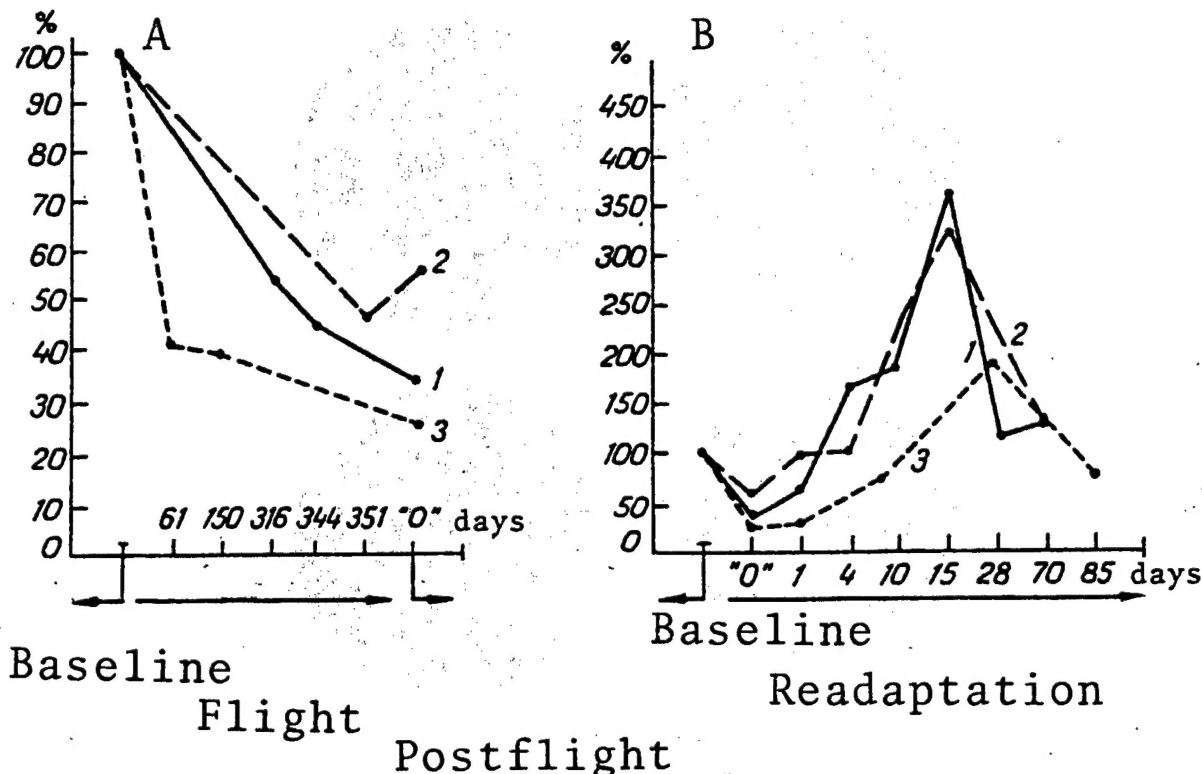


Fig. 2. Dynamics of the reticulocyte count in EO-3 crew members in weightlessness (1, TVG; 2, MMKh) on a 366-day flight and in EO-3 and -4 crew members (3, PVV) on a 241-day flight (left graph, A), and dynamics of postflight reticulocytic reaction in the same crew members.

The drop in Hb concentration in erythrocytes that is observed in the first 24 hours after landing (days 0-1) points to the depression of the synthesis of hemoglobin upon exposure to weightlessness, which may be due both to a drop in the level of erythropoietin in the blood plasma during the flight and to an iron deficiency during the flight and in the initial postflight period.

In a study of the indices associated with iron metabolism, what is noteworthy is the ambiguous iron content in the blood in the different cosmonauts and on different flights. For example, in TVG, iron content rose to 35.8 mmol/l from 27.6 in the first 24 hours after the flight, whereas it dropped to 24.4 mmol/l from 48.4 in MMKh. In MMKh, however, a drop was also noted in ferritin content in blood plasma to 3.1 mg/l from 19.6, which indicated a considerable deficiency in the supply of iron for the synthesis of hemoglobin. But that could possibly be connected with a more intense process of erythropoiesis in the flight engineer, which is indicated by a higher level of erythropoietin in the blood plasma in that period and a very pronounced reticulocytic reaction. Noteworthy in a study of those same indices of iron metabolism in EO-2 crew members (RYuV and AAP) is their substantial drop. In RYuV, serum iron content was

16.6, 17.6, and 19.2 mmol/l on days one, nine, and 65 against a baseline of 26.3 mmol/l; in AAP, it dropped only on day nine, to 16.8 mmol/l against a baseline of 21.6.

Analysis of indices for short- and long-duration flights has made it possible to establish a dependence between the restoration of erythropoiesis in the period of readaptation and the profoundness of its inhibition stemming from the duration of exposure to weightlessness. That was especially apparent in RYuV. Despite the pronounced quantitative and qualitative changes in the erythron on days 0 and 9 after landing, the plasma erythropoietin level in that period did not exceed 70 ME/ml, whereas on the short-duration flights, it ranged from 300 ME/ml to 600 for that period.<sup>2, 6</sup> The reticulocytic reaction in RYuV during readaptation was also weak, and then by day 65 there was a trend toward erythrocytosis, when the number of erythrocytes was  $6.3 \times 10^{12}/l$ , Hb was 179 g/l, and Ht was 50 percent. Normalization of hematologic indices was observed only by day 111.

A different picture formed for the period of readaptation in the EO-3 crew members. The blood plasma levels of erythropoietin on day one after landing was nine- to

12-fold higher than baseline in both cosmonauts: In TVG, it was  $380 \pm 85$  ME/ml; in MMKh,  $500 \pm 100$  ME/ml. As can be seen, those are similar to the data for short-duration flights. Later, the EO-3 crew members showed a gradual rise in number of reticulocytes, which matched the time of the high erythropoietic activity of the blood serum. That gravity-dependent reticulocytic reaction was pronounced (125 percent on days 5 and 9 and 238 percent on day 11), but, unlike the other long-duration flights, it was not as lengthy in time. In the postflight period, the reticulocytic reaction in all cosmonauts usually grew more intensely and then dropped gradually over 1.5-3 months, by which time almost complete restoration of all the other blood indices was restored. In the EO-3 crew members, it reached the physiological norms by the end of the first month of readaptation (Fig. 2, right graph, B): the reticulocyte count in TVG was 7.35 0/00 on day 28; in MMKh, 16.6 0/00; baseline was 7.0 0/00.

Activation of erythropoiesis when iron metabolism parameters are changed and plasma erythropoietic activity is high was reflected on day one of the postflight period in the morphological data associated with the alteration of erythrocytes. For example, during the first 24 hours, changes were detected in their size, changes that differed, however, in terms of a number of indices in the cosmonauts. MMKh had two populations of red cells (7.2 and 8.3  $\mu$ g). The relationship of the peaks of those cells did not change appreciably. But on day 2, small cells appeared (6.0  $\mu$ g), and on day 12, large cells (8.5  $\mu$ g and larger than 10  $\mu$ g), which is a manifestation of compensatory reactions. In TVG, the compensatory reaction was poorly pronounced, and the increase in erythrocyte Hb was not observed until day 12.

The absence of a marked depletion of iron, as was sometimes noted in earlier long-duration flights, as well as the presence of adequate erythropoietic response in the period of readaptation, is established, as a rule, in cosmonauts who, for maintaining stable physical conditions, worked out on the exercise machines at least two hours a day in orbit, which is what the EO-3 crew did faithfully. At the same time, working out on the machines is tiring for the cosmonaut, is physically difficult, and takes a lot of time. Working out on them, nevertheless, is necessary to keep the body in optimal physical condition and at an optimal efficiency, because other, more natural preventive means (artificial gravity) are not yet available.

One would have expected a higher level of erythron functioning among the EO-3 crew, with its intensive

muscular exertion in weightlessness, than among crews on other long-duration flights, in which cosmonauts devoted less attention to working out on the exercise machines. But that did not happen. Reticulocytic reaction during the flight indicated pronounced inhibition of erythropoiesis, although erythron restoration during the period of readaptation was much easier for the EO-3 crew in a number of areas (iron metabolism, erythropoietic response) and was closer to that noted for flights of 96 days or less. In addition, such a rapid normalization of hematological indices in them in the postflight period does not preclude a rapid depletion of erythron compensatory capabilities.

Thus, the results of the study of the peripheral blood of the cosmonauts indicates a need for further integrated study of the hematological problem of long-duration space flights. The absence aboard manned space complexes of natural and reliable preventive means such as artificial gravity dictates the need for determining threshold values of the adaptational reduction of erythron functioning in weightlessness.

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**Lipid Metabolism in Rat Tissues During Chronic Exposure to Gamma Radiation and Ubiquinone Q-9**

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after revision 15 Jul 91) pp 531-538

[Article by Ye. G. Novoselova, Cellular Biophysics Institute, Russian Academy of Sciences, Pushchino, Moscow Oblast; UDC 577.125]

[Abstract] The possible involvement of the natural antioxidant ubiquinone Q-9, which exerts a radioprotective effect, in processes of regulating lipid metabolism in lymphoid organs was investigated on male Wistar rats (60 g) exposed to 0.129 Gy/day for a total  $^{137}\text{Cs}$  dose of 8 Gy. The experimental cohort was given 8 mg/kg ubiquinone per day, five times per week. Measurement of lipid quantities two months later, after chronic exposure of 8 Gy, revealed no significant changes in neutral lipid metabolism. However, there were increases in the amounts of phosphatidylcholine, phosphatidylserine, phosphatidylinositol, and cardiolipin. The results also demonstrated that chronic irradiation increased the quantities of mono- and diglycerides in the spleen and activated the synthesis of diglycerides and free fatty acids in the splenocytes. Ubiquinone was shown to normalize radiation activation of the splenocytes of irradiated rats. The data indicated that feeding chronically irradiated rats ubiquinone Q-9 increases the ubiquinone concentration in the spleen three-fold, which explains the regulating effect of this antioxidant. The use of ubiquinone suppresses the intensity of incorporating the label into the lipids in bone marrow cells of irradiated rats. In conclusion, this study showed that the use of ubiquinone Q-9 as a food additive to the rat diet under conditions of chronic exposure suppresses the intensity of incorporating the labeled precursor into the cholesterol and phospholipid molecules in the lymphoid cells and also normalizes the lipid concentrations in the cells. The results of this and other studies also suggest that ubiquinone Q-9 may activate the rat immune system. Tables 6; references 14: 6 Russian, 8 Western.

**Study of Damage-Induced Proteins in Potato Plants and Their Ability To Inhibit Activity of Exogenous Serine Proteinases**

927C0515D Moscow BIOKHIMIYA in Russian  
Vol 57 No 4, Apr 92 (manuscript received 18 Jul 91)  
pp 567-573

[Article by M. V. Nesterenko, V. A. Mosin, and M. F. Shemyakin, All-Union Agricultural Biotechnology Scientific Research Institute, All-Union Academy of Agricultural Sciences imeni V. I. Lenin, Moscow; UDC 577.1]

[Abstract] The objective of this investigation was to isolate, purify, and characterize exogenous proteinase inhibitors in Nevskiy variety potatoes. The protein inhibitor preparation was isolated from potato tubers,

and antibodies to serine proteinase inhibitors were then obtained after immunizing rabbits. The results showed that the protein preparation of inhibitors effectively suppressed the activity of chymotrypsin, trypsin, and subtilisin. Mechanical damage to the plants increased the level of protein inhibitors, which peaked nine to 10 hours after the first damage was sustained and totaled 300  $\mu\text{g}/10\text{ g}$  plant tissue. The results of isoelectric focusing of protein fractions showed that most proteins from the original preparation bound with chymotrypsin-sepharose, some sorbed on trypsin-sepharose, and only two bound with subtilisin-sepharose. Data obtained by means of electromigration showed that protein 1 (universal inhibitor of all three proteinases) and protein 2 (inhibits subtilisin and chymotrypsin) have similar molecular masses. The purified protein inhibitors were found to effectively suppress the activity of hydrolytic enzymes. Protein 1 suppressed chymotrypsin and subtilisin while protein 2 suppressed all three proteinases. The inhibitor proteins isolated by Soviet and American scientists differ considerably in their physico-chemical properties, which indicates their clearly pronounced varietal polymorphism. The varietal polymorphism and physiological connection between some protein inhibitors and pest resistance in plants provide the foundation for recommending that analysis of this group of proteins be used in potato breeding. In conclusion, the isolated genes of these inhibitors may be of use in gene engineering aimed at creating a line of plants with enhanced resistance to pests. Figures 5; tables 1; references 24: 1 Russian, 23 Western.

**Effect of Monoclonal and Polyclonal Antibodies to Peroxidase on Coupled Peroxidation of 4-Iodophenol With Luminol and 4-Aminoantipyrine**

927C0515E Moscow BIOKHIMIYA in Russian  
Vol 57 No 4, Apr 92 (manuscript received 04 Sep 91)  
pp 604-616

[Article by A. V. Litvinchuk, D. I. Metelitsa, M. I. Savenkova, T. V. Cherednikova, B. B. Kim, and V. V. Pisarev; Bioorganic Chemistry Institute, Byelarus Academy of Sciences, Minsk; Biochemistry Institute imeni A. N. Bakh, Russian Academy of Sciences, Moscow; Chemistry Faculty, Moscow State University imeni M. V. Lomonosov; UDC 577.152.2]

[Abstract] The effect of three types of monoclonal antibodies to different domains of peroxidase and polyclonal antibodies against it, and binary and triple mixtures of monoclonal antibodies to the peroxidation of two pairs of substrates, aminoantipyrine-*n*-I-PhOH and luminol-*n*-I-PhOH, at 0.01-10.0 mM, with antibody concentrations in the reaction mixtures ranging from 0.05 to 500 nM, was compared. The objective of this study was to accurately compare and assess all possible pathways of the effect of monoclonal and polyclonal antibodies on peroxidase activity in reactions of the cooxidation of *n*-I-PhOH with two different amines, luminol and aminoantipyrine. It was shown that the three types of



monoclonal antibodies activate the process of oxidizing the luminol-*n*-I-PhOH pair to different degrees at H<sub>2</sub>O<sub>2</sub> concentrations of 5 and 10 mM. The results demonstrated that the activating effect of polyclonal antibodies during peroxidation at high concentrations of H<sub>2</sub>O<sub>2</sub> is more effective for the aminoantipyrine-*n*-I-PhOH pair than for the luminol-*n*-I-PhOH pair. The following conclusions were reached: 1. the antibodies activate horseradish peroxidase only at high concentrations of H<sub>2</sub>O<sub>2</sub>; 2. all factors that decrease horseradish peroxidase dissociation to the apoenzyme and heme favor the activating effect of the antibodies on horseradish peroxidase; 3. the effect of the antibodies on aminoantipyrine and *n*-I-PhOH oxidation may be opposite to their effect on the oxidation of the luminol-*n*-I-PhOH pair; 4. the horseradish peroxidase-polyclonal antibody complexes are probably much stronger than the horseradish peroxidase-monoclonal antibody complexes and differ in their molecular composition. Figures 5; tables 4; references 26: 16 Russian, 10 Western.

#### **Modification of Rat Thymic Lymphocyte Radiosensitivity With Cholesterol-Enriched Autoliposomes**

927C0518C Moscow BYULLETen  
EKSPERIMENTALNOY BIOLOGII I MEDITSINY  
in Russian Vol 113 No 2, Feb 92 (manuscript received  
17 Nov 90) pp 136-138

[Article by V. S. Posokhov, O. A. Rozenberg, and K. P. Khanson, X-Ray Radiology Central Scientific Research Institute, USSR Ministry of Health, Oncology Scientific Research Institute imeni N. I. Petrov, Leningrad; UDC 616.438-008.953.2-02:616-001.28]-092.4]

[Abstract] The possibility of modifying the radiosensitivity of thymic lymphocytes by enriching them with cholesterol-bearing liposomes was investigated using lymphocytes extracted from the thymuses of albino mongrel rats (120-130 g). It was shown that irradiating the thymocytes with a 10 Gy dose causes a significant increase in the formation of polydesoxyribonucleotides, which indicates an increase in chromatin degradation. However, cholesterol enrichment of the thymocytes was shown to hinder chromatin degradation and the formation of polydesoxyribonucleotides in a dose-dependent fashion. It was also demonstrated that the radiosensitive effect of cholesterol-bearing autoliposomes is displayed only when the cells are enriched with cholesterol prior to radiation exposure. Cholesterol is not an anti-oxidant, but in the membrane it increases the packing of fatty

acid chains of phospholipids, making oxygen diffusion difficult and suppressing the onset of lipid peroxidation. Thus, it has been shown for the first time that an increase in the cholesterol level in thymocytes increases their resistance to the effect of ionizing radiation. These results indicate that cholesterol-bearing liposomes may be an effective means of modifying the radiosensitivity of cells. Figures 3; tables 1; references 15: 9 Russian, 6 Western.

#### **Effect of Antioxidant Emoxypine on Pulmonary Lipid Metabolism During Development of Pulmonary Edema**

927C0518D Moscow BYULLETen  
EKSPERIMENTALNOY BIOLOGII I MEDITSINY  
in Russian Vol 113 No 2, Feb 92 (manuscript received  
19 Jul 91) pp 139-141

[Article by V. P. Mikhaylov, L. D. Smirnov, G. V. Kurygin, and N. N. Zolotov, Pathophysiology Chair, Yaroslavskiy State Medical Institute; All-Union Science Center for the Safety of Biologically Active Substances, Kupavna, Moscow Oblast; UDC 616.24.005.98:-02:618.8:547.823(-036-092.9)]

[Abstract] The effect of the water-soluble anti-oxidant emoxypine on pulmonary lipid metabolism against a background of pulmonary edema was investigated in 30 albino male rats administered 100 mg/kg of the anti-oxidant for four days. Pituitrin (10 µg/kg) was employed to induce pronounced pulmonary edema. The results demonstrated that emoxypine pretreatment prevented a decrease in the level of total lipids, phospholipids, and non-esterified fatty acids normally caused by pituitrin, but it facilitates a further (17.3 percent) decrease in the cholesterol level. It was shown that the membrane-stabilizing effect of emoxypine on the lungs with suppression of lipid peroxidation processes in them is accompanied by the development of more pronounced pulmonary edema. In addition, the data indicated that suppression of pulmonary lipid peroxidation processes in response to edemogenic factors induced by activation of these processes may elevate pulmonary edema activity. In conclusion, it is likely that emoxypine, by preventing the accumulation of hydrolyzed radicals of phospholipids and free fatty acids and by suppressing lipid peroxidation, enhances the effect of interaction between the receptor and ligand, which is expressed as a more pronounced response reaction to stimulating factors. Tables 1; references 15: 13 Russian, 2 Western.

**Sodium Channel Blockers Quinidine, Flecainide, Ethmozine, and Ethacizine Effectively Block Calcium Current in Frog Heart Cell**

927C0515B Moscow BIOLOGICHESKIYE  
MEMBRANY in Russian Vol 9 No 4, Apr 92  
(manuscript received 27 May 91) pp 367-375

[Article by B. S. Marinov, F. Skamps, and A. I. Undrovinkhs; Theoretical and Experimental Biophysics Institute, Russian Academy of Sciences, Pushchino, Moscow Oblast; Laboratory of Cellular Cardiology Physiology, Paris University, France; All-Union Cardiology Research Center, Russian Academy of Medical Sciences, Moscow; UDC 577.352.465]

[Abstract] The ability of the antiarrhythmic substances quinidine, flecainide, ethmozine, and ethacizine to block  $I_{Ca}$  in single frog (*Rana esculenta*) cardiomyocytes was

compared on the basis of their electron donor properties using the patch clamp method. The results showed that ethacizine was most effective in blocking  $I_{Ca}$ , with quinidine, flecainide, and ethmozine shown to be less effective, in that order. However, when a frequency-dependent block was involved the sequence was: ethacizine > ethmozine >> quinidine > flecainide. The data also showed that these substances are electron donors in radical reactions, but they are also able to block sodium and calcium channels. In addition, the results indicated that the electrical charge acquired under physiological conditions prevents the substances from penetrating the membrane. In conclusion, the effectiveness of ethacizine and ethmozine in blocking the channels and inhibiting the  $I_{Ca}$ , even in a frequency-dependent manner, is attributed to their electron donor properties. Figures 5; references 12: 1 Russian, 11 Western.



**Republic Scientific-Practical Conference 'Mental Aftereffects of Chernobyl AES Accident'**

927C0481A Minsk ZDRAVOOKHRANENIYE  
BELORUSSII in Russian No 3 (84) Mar 92 pp 71-72

[Article by Prof. F. M. Gayduk, Cand. Med. Sci. V. D. Korolev, Minsk; UDC 612.014.482:616.89]:061.3(476)]

[Text] On 26 June 1991, at the Minsk Medical Institute, the first republic scientific-practical conference—"Mental Aftereffects of the Chernobyl AES Accident"—took place. Taking part in the work of the conference were psychiatrists, psychologists, psychotherapists, sex pathologists, directors of psychiatric facilities, and other specialists. At the conference, an analysis was given of the mental state of the people living in the rayons that suffered as a result of the Chernobyl AES accident, aspects of the rendering of practical assistance to the population were discussed, and the principal directions to be taken in the work of psychiatrists were outlined. Ten papers were read.

Cand. Med. Sci. V. D. Korolev, the chief psychiatrist of the republic's health ministry and head of the laboratory for the study of the mental consequences of the Chernobyl AES accident, reported that information on mental morbidity and illness in rayons under strict monitoring is ambiguous and requires further analysis and study. According to his data, the per-1000-population morbidity rate associated with nervous-mental disorders in Mogilev Oblast grew twofold in 1989. An increase in the number of individuals with neuroses was noted in Gomel Oblast as early as in 1987.

According to the data of Prof. Yu. A. Aleksandrovskiy, G. M. Rumyantseva, V. V. Yurov, and A. N. Martishov (All-Union Scientific Research Institute of General and Forensic Psychiatry imeni V. P. Serbskiy), borderline disorders are noted in 95 percent of the residents (neuroses account for 22.4 percent of cases; neurosislike manifestations, 25.7 percent; accentuation of character, 8.9 percent; and preclinical forms of mental deadadaptation, 38 percent).

In 1990, a group of specialists led by Prof. V. T. Kondrashenko studied patients for 10 days at the clinic of the Belorussian Scientific Research Institute of Radiation Medicine and found definite nervous-mental disorders in most of them. V. D. Korolev identified numerous stress-causing factors in the rayons stricken by the radiation and noted that often radiophobia was helped along by the medical workers, who sometimes were poorly versed in radiation medicine, and by contradictory reports in the press.

The address given by Prof. F. M. Gayduk was devoted to organizational and procedural aspects of research in the field of radiation psychiatry. He analyzed the principal possible pathogenic effects that radiation and radiation danger have on the human psyche, which should determine the main directions to be taken by research. Damage to the hereditary apparatus could be the source of congenital oligophrenia, and the action of radiation on the brain could

cause a psychoorganic syndrome; chronic psychoemotional stress is the source of borderline disorders and psychosomatic illnesses. Of some urgency is the problem of somatopsychic and psychosomatic interrelationships. The effects of small doses of radiation on man are not understood clearly enough. The data of various authors on the interrelationship of neurotic and psychoorganic disorders among people in rayons under strict monitoring are contradictory.

Requiring especial attention are children born of mothers whose pregnancy occurred during the time of the Chernobyl accident. Prof. Gayduk, in analyzing the research in the republic, noted that appropriate studies are being conducted by a few interested researchers only, without the proper financing. There is no coordination or continuity of research, the research is not systematic, and there is no single methodological approach. Gayduk made a number of constructive suggestions and urged that all research work done in rayons under strict monitoring have a practical side, in addition to having purely scientific aims.

A great deal of interest was elicited by the paper given by G. K. Kraynov et al. on the topic, "Analysis of psychopathology in today's ecological situation in Mogilev Oblast." I. A. Beller, head of the organizational-procedural office of the oblast psychiatric hospital, noted that the figures for morbidity due to schizophrenia, epilepsy, and various psychoses had stabilized; it was noted that they had even declined as a result of the introduction of new principles for recordkeeping for the mentally ill.

At the same time, in rayons under strict monitoring, visits to doctors had increased for neurocirculatory and vegetovascular dystonias and for asthenic and asthenoneurotic states. In Krasnopol'skiy Rayon, for example, those pathologies were identified in dispensary examinations in 7.5 cases per 1000 in 1986, in 35.1 per 1000 in 1987, and in 65.3 per 1000 in 1988. Borderline nervous-mental disorders are encountered 3-3.5 times more among women than among men. More often than not, the individuals with such complaints are over 30 years of age. A growth in borderline disorders has also been noted in children, especially in young girls in prepuberty or at puberty. Children complain most often of headaches and fatigue. Teachers note that schoolchildren are less active and are slower. Especially negatively affected are children who stay in school for 12 hours. The speaker cited the results of a survey of the residents of six villages, which revealed that most of the people do not go to the doctor for headaches and fatigue, but treat themselves. Beller spoke of the specific measures adopted by the psychiatric service of the Mogilev Oblast to improve assistance for the population. However, he named many problems that the psychiatric service cannot resolve without the assistance of the oblast executive committee, other local agencies, and the republic health ministry. In particular, psychotherapy offices need to be created in all rayons under strict monitoring and at polyclinics and general hospitals of the cities of Mogilev and Bobruysk. The opening of the psychosomatic department at the Mogilev hospital is being delayed, as are the opening of the department of borderline conditions at

the old building of the hospital for the disabled of the Great Patriotic War and the opening of a children's/teenage psychiatric center. The oblast needs psychotherapists and psychologists. An oblast psychiatric hospital needs to be built, and a psychiatric department at the Bobruysk City Hospital needs to be set up.

The papers by A. E. Kachalko and I. M. Zheldak reported that in children 12-15 (from the city of Khoyniki), elevated emotional lability and alarm are encountered consistently more often, which, in the view of the speakers, could be largely due to disruption of the function of the thyroid gland and could reflect mental and emotional stress in families. It was pointed out that in rayons exposed to radiation, there are a considerable number of incomplete families in which the fathers have left for unirradiated rayons to build homes. The greatest emotional stress was noted in the families of doctors and teachers. It has been established that 34 percent of the children examined in the city of Khoyniki are in need of psychotherapeutic counseling. In light of the fact that in rural rayons there is a lack of pediatric psychiatrists and, even more so, of psychotherapists, the speakers proposed the positions be created for psychiatrists and psychotherapists immediately and that the activity of individual research groups without the permission of a coordinating agency be banned so as to prevent further mental injury.

S. V. Bazilchik and Ye. V. Kazak (Belorussian Scientific Research Institute of Radiation Medicine), in studying children and teenagers in the Khoynikskiy and Lelchitskiy rayons, found a consistent increase in asthenic phenomena, alarm-phobia disorders, autonomic disorders, and hypochondriac states. The speakers feel that those disorders are of a psychogenic nature, and they do not find a clear-cut dependence on radiation-factor exposure and degree of increase of thyroid gland.

The paper given by Candidate Medical Science T. V. Dokukina and Candidate Medical Science N. N. Misyuk was devoted to a comparative electroencephalographic study of patients (182) with borderline conditions from radiation-contaminated rayons and from uncontaminated rayons. Individuals who were permanent residents of rayons exposed to radiation were found to exhibit more-marked changes in the bioelectrical activity of the brain, which indicated a dysfunction of stem structures and activating systems.

Z. A. Gutkovich, in studying the incidence of congenital mental retardation among children born in the postaccident period in four affected rayons (Khoynikskiy, Vetkovskiy, Krasnopol'skiy, and Kostyukovichskiy) and in two control rayons (Kalinkovichskiy and Goret'skiy), did not find any appreciable differences in the indices.

Taking part in a discussion were Prof. Ya. L. Kolominskiy, Dr. Med. Sci. Ye. I. Skugarevskaya, Prof. M. P. Doroshkevich, D. I. Donskoy (chief psychotherapist for the city of Minsk and director of the branch of the international

institute for the study of man's reserve capabilities), D. Z. Kapustin (chief sex pathologist for the republic health ministry), and others.

At the end of the conference, a resolution was adopted.

### **Neurocirculatory Dystonia in Individuals Living in Radionuclide-Contaminated Areas and in Individuals Who Did Cleanup Work at Chernobyl After the Accident**

927C0482A Minsk ZDRAVOOKHRANENIYE  
BELORUSSII in Russian No 3 Mar 92 [manuscript  
submitted 20 Aug 91] pp 4-7

[Article by V. A. Matyukhin, Prof. I. I. Goncharik, S. S. Korytko, Belorussian Scientific Research Institute of Radiation Medicine; UDC 616.8-009.86-071]

[Abstract] The results are presented from a hospital-based study of 320 neurocirculatory dystonia patients aged 15-53 (206 men and 114 women), 203 of whom lived in a contaminated zone under strict monitoring and 107 of whom were involved in the cleanup at Chernobyl after the accident. The diagnosis was made on the basis of analysis of clinical symptoms and was confirmed with instrument-laboratory tests. The instrument tests included EKG probe with hyperventilation, orthostatic probe, and probes involving potassium chloride and  $\beta$ -blockers. The neurocirculatory dystonia patients were found to have typically wide-ranging complaints that included, primarily, chest pains (96 percent), weakness and rapid fatigue (94 percent), irritability and nervousness (82 percent), headache (81 percent), respiratory problems (80 percent), rapid heart beat (78 percent), coldness and paresthesia of the extremities (72 percent), sleep disturbances (71 percent), vegetovascular paroxysms (62 percent), and, among others, vertigo (60 percent). Objective tests revealed tachycardia in orthostasis or in hyperventilation (92 percent), episodes of high blood pressure (90 percent), systolic noise in the pericardial region (72 percent), red dermographia (86 percent), elevated dampness of the palms and armpits (84 percent), cold hands (80 percent), and, among other things, respiratory arrhythmia (72 percent). The positive functional tests in the individuals indicated a low tolerance to stressful situations and suggested general deadadaptation syndrome. Long-term use of  $\beta$ -blockers, psychotropic drugs, tranquilizers, vitamins, and procedures such as acupuncture improved their conditions. References 9: Russian.

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### **Condition of Thyroid Gland in Children and Teenagers Living in Regions of Belarus in Which Goiter Is Endemic**

927C0482B Minsk ZDRAVOOKHRANENIYE  
BELORUSSII in Russian No 3 Mar 92 [manuscript  
submitted 28 Aug 91] pp 8-12

[Article by V. F. Kobzov, A. N. Arinchin, Ye. V. Davydova, M. I. Garshanov, Belorussian Scientific Research Institute of Radiation Medicine; UDC 616.441-053.5/.7-036.2(476)]

[Abstract] A total of 598 children and teenagers (291 males and 307 females) were studied over the period of October 1989 to April 1991. The subjects were aged six to 16 and lived in Braslav, Vitebsk Oblast. The radiation characteristics of that region were as follows: average 1987-1990 natural gamma background levels outside, 10-11  $\mu$ R in winter and 11-12  $\mu$ R in summer. The subjects underwent anthropometry accompanied by an estimate of physical development, plus a clinical endocrinological examination. Results indicated that age-related tendencies associated with the change in the degree of endemic hyperplasia of the thyroid gland were preserved, i.e., a reduction in the number of children with an unenlarged thyroid and an increase in the number of children with endemic grade I hyperplasia of the thyroid. The greatest number of errors took place in determination of grade I enlargement of the thyroid via palpation (73.9 percent). The lack of correspondence of the actual physical development resulted in more than 50 percent of the errors in the use of palpation to determine endemic hyperplasia in the children whose physical development exceeded the age norm. Subjects with a thyroid size below the lower limit of the age norm in ultrasound should be considered at risk for development of thyroid pathology. References 12: Russian.

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#### Journalist Doubts Conversion of Yekaterinburg Laboratory

927C0522A Moscow MOSCOW NEWS in English  
7-14 Jun 92 p 8

[Article by Vadim Chelikov: "A Weapon Against Their Own People"; first paragraph MOSCOW NEWS comment]

[Text] The Russian President's recent Decree "On Ensuring Fulfillment of International Commitments in the Field of Biological Weapons" has indirectly confirmed what has, actually, not been a secret for some time: The Soviet Union acted for years counter to the Convention "On Banning the Development of Biological and Bacteriological Weapons" ratified by it in 1975. The authorities have still not dared to admit openly the existence of three secret centres (in Kirov, Sergiyev Posad and Yekaterinburg) where the dangerous viruses used to be grown and where a bacteriological Chernobyl occurred long before the radioactive Chernobyl.

#### Rose-Coloured Cloud

On April 4, 1979, the Sverdlovsk ambulance service operators came under a hurricane of phone calls. The calls came from the certain neighbourhoods and the symptoms given were similar: temperatures being as high as 41°C, cough, vomiting. The local hospital was soon filled to capacity, and the victims were taken to a neighbouring one. Most patients died, moreover at a moment's notice, speaking clearly and distinctly to the doctor a minute before their death. Towards evening it

became clear that the initial diagnosis—pneumonia—had been incorrect. The city had been hit by an outbreak of anthrax.

The disease hit the neighbourhoods located to the south of the so-called 19th military cantonment. The wind was blowing precisely in that direction on the previous day. Some claimed to have seen an emission in the shape of a rose-coloured cloud rising beyond a tall barbed-wire fence between 5 and 6 p.m. on the previous day. Almost the entire shift of the ceramics factory, located next to the cantonment, was taken to the hospital. And although the cantonment's leadership said that they had nothing to do with the incident, medics started answering to the calls wearing antiplague suits and gas masks. The city was panic-stricken, and relatives refused to bury their kith and kin.

During this emergency the Sverdlovsk KGB department behaved as ought to be expected. As admitted by its former chief, General Yuri Kornilov, prior to April 1979 he did not even know what the cantonment was concerned with because the latter's leadership took orders directly from the General Staff. Therefore, for two more weeks during the epidemic, the regional KGB department continued scavenging burial grounds for fallen cattle and trying to catch spies, while paying not the slightest attention to what not only the whole of Sverdlovsk but also foreign radio broadcasts were saying.

But the broadcasts demonstrated rare unanimity: In defiance of the convention, they said, the USSR was busy developing bacteriological weapons as evidenced by the outbreak of an anthrax strain in the 19th military cantonment on an outskirt of Sverdlovsk.

#### 'Meat' Version

Anthrax is a terrible weapon—not the natural one which originates from direct contact with sick animals (as a rule, it is easily cured), but its sister—developed in a test tube. For the strain attacking the lungs, the lethal outcome is not lower than 80 per cent and death is almost instantaneous—in six to eight hours.

At that time, in spring 1979, most of the cases died from the lung form which caused a brain haemorrhage of the "Hippocratic cap" type.

A State Commission led by Pyotr Burgasov, Deputy Minister of Public Health, Chief State Sanitary Physician of the USSR, arrived in Sverdlovsk. By that time the KGB department had already concluded its searches. True, they had found no spies, but a couple of Americans, who happened to be in the closed city for unknown reasons, were expelled from the country. As for the investigation of the reason of the epidemic, the vigilant bodies immediately found a peasant who had sold the meat of an anthrax-infected cow on the local market. This fact was given as the basis of the official—"meat"—version of the epidemic's origin voiced in the press by the pundits I. Bezdenezhnykh and V. Nikiforov.

If, accepting their version, it is presumed that the villagers suddenly started slaughtering their cows in spring and, bypassing the sanitary service, selling the meat on the market, then whence the lung form of the anthrax? After all, the intestinal form, as I have said above, was contracted by a few persons, quite possibly due to the meat of that same cow which security people had found (or "organized?").

Two months later the epidemic ended taking a toll of 64 human lives, according to official figures. They were buried in accordance with a special instruction of the sanitary epidemiological service in the loam of the eastern part of the cemetery, with bleaching powder poured on the coffins. On the master plans for building the city this place is marked with a red cross to prevent construction work being started here even many decades later.

#### No Help—For Want of Desire?

It is only now, eleven years later, that light is being shed on the details of that tragedy, leaving no stone unturned in the official version. Some of them have already been cited by KOMSOMOLSKAYA PRAVDA and IZVESTIA, but there are also new facts:

There is an eloquent story of an anthrax vaccine which hit people in Sverdlovsk. It was brought from Tbilisi and inoculated not only those already sick, but also all the inhabitants of adjoining neighbourhoods. It seemed that the meat of one cow had been eaten by at least 3,000 persons. Incidentally, the State Commission itself, it seems, did not have too much faith in the "meat" version. Otherwise, why would Burgasov have insisted on treating the contaminated neighbourhoods from the air, and on washing roofs with soap solution and caustic soda?

One more paradox: Among the more than 500 hospitalized persons, there were almost no inhabitants of the 19th cantonment itself. It would seem that this absolves the secret laboratory from the slightest suspicions. The contrary is, alas, the case.

Under somewhat clandestine circumstances I got hold of an ampule full of a dark brown liquid manufactured in the cantonment. In the ampule was live anthrax vaccine. When I phoned Anatoly Kharchenko, chief of the cantonment, he said with pride that their liquid vaccine was much more effective than the dry one from Tbilisi. "Regrettably," the general observed, "we no longer produce it." He also lamented that in 1979 the military had not been involved in combatting the epidemic. "It's a pity—we could have rendered real assistance."

The point is that in April 1979 all of the cantonment's inhabitants and personnel were inoculated with the liquid, local vaccine. It was all the more effective as it had been grown from the kind of anthrax which was affecting the citizens. The vaccine did not go any further than the cantonment, and the rest of Sverdlovsk inhabitants were inoculated with the Tbilisi vaccine—hardly suitable for those conditions. Moreover, another seven persons lost their lives due to it. During the autopsy the

vaccinal strain, in addition to the main one, was found in these people, it had aggravated the disease.

I have at my disposal the text of ex-Defence Minister Dmitry Yazov's reply to an inquiry from Oleg Kravets, deputy to the Sverdlovsk City Council. Yazov writes: "The above-mentioned facility in Sverdlovsk (the 19th cantonment) is a structural subunit of the Research Institute of Microbiology under the USSR Ministry of Defence—a sector of military epidemiology. This institution concerns itself with work in the field of the antibacteriological defence of troops and the population, notably, developing methods and means for the disinfection of terrain, military hardware, weapons and equipment, means for protecting people against biological aerosols and for the early detection of noxious substances in the environment."

It sounds solid, doesn't it? But we know that terrain disinfection was carried out not by the cantonment's specialists, but by Burgasov's Commission which unprofessionally raised contaminated dust into the air by its washing of roads and thus caused a new wave in the epidemic. Due to improper disinfection, the anthrax was not wiped out in Yekaterinburg—it hid itself in the soil which was rolled over with asphalt and is waiting.

Thus, the culprits were reluctant to become rescuers, for which many of the unsuspecting people paid with their health or even lives. Non-rendering of aid, as we all know, is also a crime. Although everything can be simply explained: the military were sitting snug to ward off suspicion.

#### No More Secrets?

Today security people are extremely outspoken. According to their information, the tragedy occurred because one of the secret laboratory's staff members started work, forgetting to switch off the electronic filter for the ventilation system thereby scattering the anthrax over a vast area. Yuri Andropov was said to be drafting a resolution on compension to citizens who suffered during the epidemic. This resolution, unrealized at that time, has been embodied in Boris Yeltsin's April Decree "On Improving Pension Maintenance for the Families of Citizens Who Died in Consequence of Falling Ill With Anthrax in Sverdlovsk in 1979."

But General Kharchenko has stubbornly continued denying his centre's involvement in the above-mentioned events. When I made reference to the state security service, he irritably advised security people to mind their own business and not discredit the army. According to his words, the cantonment is now geared exclusively for medical needs and is going to produce antibiotics and artificial blood substitutes. All this is wonderful, but for some reason he did not permit me to visit this strictly peaceful scientific laboratory—this, he said, requires permission from the General Staff.

I have been to the cantonment nevertheless—without the general's help, it is true. Three- and five-story houses, a copy of a Moscow project, stand behind the fence. Its

population is roughly between 10,000 and 15,000. The entrance to the territory is guarded by soldiers, and armed patrols with dogs are pacing the strip along the fence at night. Of late the place has been covered by people interested in making it a co-op—there is neither racket nor thieving. The secret laboratory is enclosed in a separate fence with barbed wire, and a special pass with a multitude of stamps is required to get in. Incidentally, considering the amount of crime in Yekaterinburg, the idea of removing the guard has evoked protests from the cantonment's inhabitants themselves. Although there is virtually no need for him, once bacteriological weapons are no longer being developed there.

#### Query Instead of Fullstop

To "confess," "repent," "punish"—are these most important things to do? Recall that, first, anthrax has not been eliminated in the Urals. Second, according to some information, the death laboratory is still alive—it has merely changed its location. Who can vouch that an epidemic, the source of which cannot be easily explained, will not break out tomorrow somewhere not far from Irkutsk? After all, an outbreak of plague, which hit a herd of yaks, did occur not long ago on the border with Mongolia. In short, instead of a full-stop, a query is still appropriate. Will this story be continued?



**Participation of *Mus musculus* (*Rhodentia*, *Muridae*) in Epizootics of Plague in the Northern Aral Region**

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[Text] *In an epizootological investigation in the Northern Aral region (from Northern Ustyurt and Predustyrtye to the trans-Aral region), 38 strains of plague agent were isolated from house mice and their fleas in 1945-1988—among them, 27 in population centers, and 11 in the field. The mice were most often infected during years in which their population was large and natural plague foci were activated. Infected mice were found most often in the Aral-region Karakumy—the most active plague focus in the Northern Aral region. Systematic settlement-by-settlement rodent extermination is a necessary part of the prevention of plague in natural foci.*

The house mouse is a widespread and often large-population species. In the natural Central Asian desert focus of the plague, which includes the Northern Aral region (in the broad sense of the word, from Northern Ustyurt and Predustyrtye in the west to the trans-Aral region and the northern Karakumy inclusive in the east), that species is considered a secondary carrier of plague. The epidemiological significance of the house mouse is rather great in view of its inherent synanthropy and habitation in arid zones both in population centers and in the field, its seasonal migrations from open habitats to enclosed habitats (Varshavskiy, 1937; Sheykina, 1940; Soldatkin et al., 1959; Smirin, 1960; etc.), and its contact with populations of rodents of other species that live in the wild. In fact, in the desert regions of the Northern Aral region, no pronounced seasonal migrations of house mice are recorded, and only seasonal regroupings of them within population centers are noted (Burdelov et al., 1986). But in light of the nature of the population centers of that zone (the establishment of rodents that are the main carriers of plague on their outskirts—particularly, the placement by large gerbils of their burrows near outdoor structures, adobe fences, hay and fuel storage areas, etc.) those (intrasettlement) movements of the house mice could have a rather large epidemiological significance as a result of contact with wild rodents.

The house mouse is known to be highly sensitive to the plague in any season, but especially in the fall (Shiryayev, 1957).

The first bacteriologically confirmed epizootic of plague among house mice was recorded in 1913 in Ural Oblast by Koltsov (1916) and Tikhomirov (1926). There is also

no doubt that the plague epidemics between 1900 and 1913 in the Volga-Uralsk sands and Ural lowlands arose in connection with epizootics among mouselike rodents (Shiryayev, 1958). Subsequently, plague epizootics in populations of house mice were registered in the southeastern part of the USSR almost every year until 1939, with the exception of 1928-1931 (Nikanorov, 1922; Tikhomirova et al., 1935; Shiryayev, 1958). An epizootic that was especially widespread occurred in 1932-1933 in Rostov Oblast and Stavropolskiy Kray, and it arose against the backdrop of a massive growth in the population of mouselike rodents and the accompanying human disease.

Later, Myalkovskiy et al. (1983) noted the isolation of one strain of plague agent from house mice in 1980 in the Nogay Steppe. Of especial interest is the frequent participation of house mice in plague epizootics in the southeastern part of the Caspian northwestern steppe, which began in 1979 in the vicinity of Artyezh Station, against the backdrop of a sharp decline in the population of regional species of rodents (Ilyukhin et al., 1983; Lavrovskiy et al., 1983).

It is noteworthy to recall the 1937-1938 epizootic among house mice and other rodents in the Volga-Akhtubinsk floodplain (Fenyuk et al., 1959), as well as the 1958-1959 epizootic in the Ural lowlands (Fenyuk et al., 1962).

Plague epizootics among house mice have appeared only in years in which their population burgeoned against the backdrop of epizootics among communities of the main carrier—the small large-toothed souslik (Fedorov, 1944; Fenyuk, 1948). In other cases, however, only the involvement of mice in the epizootic process taking place in populations of other rodents has been observed.

Infection of house mice with the plague in nature takes place when they come in contact with regional species of rodents—the main carriers of the infection. For example, contacts between the house mouse and the great gerbil in the Northern Aral region were established by the observations of Shutov (1974) and Burdelov (1974). Tlegenov et al. (1974) reported about the house mouse frequenting the burrows of the tamarisk and midday gerbils, and Demyashev (1964), about the house mouse frequenting the burrows of the yellow souslik.

The literature describes only a few cases involving the identification of sick house mice in the Central Asian desert plague-focus (undoubtedly, the features of the range and population dynamics of the mice inhabiting the desert biotopes have an effect on that). For example, Lankin (1978) reported the isolation of plague cultures in two mice cause in June 1948 on the Buzachi Peninsula in dwellings in the settlement of Tushchekuduk. In September 1969, the Guryev mobile plague station isolated two cultures of plague agent from two house mice in Zapadnyy [Western] Ustyurt during an epizootic in a great-gerbil community along the railroad line (Nastyukov et al., 1971). In the autumn of 1972, the Chimkent plague station got one strain of plague agent

from a group of house mice from the settlement of Furmanovka in the Prichuysk Mnyunkumy (Bykov et al., 1974). In the spring of 1975, one culture of plague agent was isolated from a house mouse caught on a railroad track embankment 10 km to the west of the Makat station of the Guryev railroad line (Nastyukov et al., 1984).)

The house mouse in the Northern Aral region, located mainly in the northern subzone of the desert is, unlike the house mouse in the southern subzone, rather widespread and inhabits most of the biotopes that have mesophyll plants, and its population in favorable years is rather large (Shilov, 1960, 1988; Marin, Leonov, 1962).

No special captures of house mice for bacteriological study were made before the autumn of 1988, and rodents caught for purposes of determining their population size or during extermination were the rodents that were brought into the laboratory. At each observation point, along with the capture and recording of the main carriers of the plague, no less than 100 traps were set up to record the population size of small mouselike rodents. There have been no dramatic variations in the volumes of epizootic observation in the various years, which is why the results of such observation are entirely comparable in perennial terms. The specific figures are as follows. From 1946 through 1960, the Aral Sea station studied 673,469 small mammals, including 55,636 house mice (8.3 percent). In individual years, the absolute numbers ranged from 847 (1948) to 6,032 (1959), and the relative figures ranged from 8.3 percent (1948) to 15.2 percent (1946). The percentage of mice caught in the field, from a sample covering four years, was 10.3 percent (1,575 of 15,334) of all the rodents studied here over that period. House mice caught in open habitats constituted 0.8 percent.

The first reports about the involvement of the house mouse in plague epizootics in the Northern Aral region are contained in papers written by Besedin (1963) and Yeremitskiy et al. (1963).

We examined materials on plague-agent cultures isolated from wild mammals around the Aral Sea station and the Kzyl-Orda station, as well as by the Kazalinsk mobile plague station, between 1945 and 1988.

Over that period of time, 10 years are noted in which the involvement of the house mouse in plague epizootics is recorded (1947, 1950, 1957, 1958, 1962, 1963, 1965, 1975, 1980, 1988). All those years are characterized by an intense flow of epizootics either on the greater part of the independent foci located here or right in the region in which the plague mouse was found (92-598 strains, with an average of 326 over the 10 years for all the Northern Aral region; 19-629 strains, with an average of 250 over the period 1945-1988).

The year 1988 should be singled out because 11 plague-agent cultures were isolated from house mice and their fleas (over the previous 42 years, 27 strains were gotten), and all of the cultures were isolated in the Aral-region Karakumy.

The year 1988 also saw 13 positive serological reactions from house mice from 10 points, with one reaction from the northern shore of the sea (northern Priaralye autonomous focus) and the rest from the Aral-region Karakumy.

It is instructive that 1988, which had a high epizootic activity focus, was preceded by seven consecutive years of unusually low activity. For example, if 1980 was almost a record in terms of the appearance of plague epizootics (598 cultures of plague agent for the Northern Aral region as a whole), then between 1981 and 1987, plague cultures for that area numbered only 262, 118, 97, 67, 25, 57, and 61, respectively. The low activity of the focus was observed against the backdrop of a small great-gerbil population in a number of areas of the Northern Aral region, a population that gradually increased until 1988. In the Aral-region Karakumy, in particular, where most of the strains were isolated (333 of 418 for all of the Northern Aral region), the 1988 population of the great gerbil was higher than that of the previous year and the average perennial figure.

An even more important factor for the multiple involvement of house mice in the acute plague epizootics that took place among great gerbils and nine other species of small mammals is the considerable increase in their number in 1988, especially in the Aral-region Karakumy and the near-delta part of Syr-Darya, which was helped by the increase moisture levels in the region (filling dry channels and lakes with water). Although over the year in the field habitats of that region the average number of house mice did not exceed 1.1-1.2 percent of the animals that got into the traps, in some areas the number was as high as 9-17 percent. In the autumn, in places, there was a high level of reproduction of mice, who at night could be encountered even on asphalt roads. In gardens, cucurbit fields, and hay fields, mice could be seen even in the daytime.

The number of house mice grew in human population centers, and in most of the Aral-region Karakumy, the average percentage of those that got into the traps was 20.9-22.7 percent in the autumn (with a maximum of 66.5 percent).

Also playing a large role in the spread of plague infection among house mice in population centers was, apparently, the fact that hay was cut from the epizootic territory for private farms, and that hay probably contained plague-infected house mice and shrews.

It should also be noted that in the autumn of 1988, the Aral Sea station recorded the population and the number of catches of house mice, as a result of which several hundred of those rodents were studied in the laboratory.

All the instances of the isolation of plague-agent cultures from the house mouse in 1988 also were tied to the autumn, primarily September (only one strain was gotten from a mouse caught in October). Seropositive reactions were also gotten in the autumn (in September and October, and one each in November and December).



For the other years in which the involvement of the house mouse was recorded in the epizootics of the plague, a high epizootic activity of focus (considerably higher than the average) was typical. In 1947 and 1950,

although epizootic activity was low for the Northern Aral region as a whole, it was high or even very high for autonomous foci (northern Priaralye and the trans-Aral region) (see the table).

**Involvement of the House Mouse in Plague Epizootics in Autonomous Foci of the Northern Aral Region, 1947-1988**

| Year                 | Autonomous focus                  | Plague-agent cultures isolated                              |           |                               |                     | Percentage of cultures from house mouse, in percent |  | Number of points with plague-infected mice |              |
|----------------------|-----------------------------------|---|-----------|-------------------------------|---------------------|---|--|--|--------------|
|                      |                                   | For northern Priaralye as a whole for the years in column 1 | Including |                               |                     | Of the total number of cultures                     | Of the number of cultures for the autonomous focus | In buildings                               | In the field |
|                      |                                   |   | Total     | From house mouse or its fleas |                     |   |  |  |              |
|                      |                                   |   |           | Total                         | Caught in the field |   |  |  |              |
| 1                    | 2                                 | 3   | 4         | 5                             | 6                   | 7   | 8  | 9  | 10           |
| 1947                 | Northern coastal zone of Aral Sea | 168   | 106       | 10                            | 0                   | 6.0   | 9.4  | 1  | 0            |
| 150                  | Trans-Aral region                 | 98  | 14        | 1                             | 1                   | 1.0   | 7.1  | 0  | 1            |
| 1957                 | Aral-region Karakumy              | 92  | 84        | 1                             | 1                   | 1.1   | 1.2  | 0  | 1            |
| 1958                 | Aral-region Karakumy              | 310   | 251       | 1                             | 1                   | 0.3   | 0.4  | 0  | 1            |
| 1962                 | Northern Kyzylkumy                | 447   | 18        | 3                             | 0                   | 0.7   | 16.7   | 2  | 0            |
| 1963                 | Trans-Aral region                 | 519   | 75        | 1                             | 1                   | 0.2   | 1.3  | 0  | 1            |
| 1965                 | Aral-region Karakumy              | 309   | 24        | 4                             | 1                   | 1.3   | 16.7   | 2  | 1            |
| 1965                 | Northern coastal zone of Aral Sea | 309   | 39        | 1                             | 0                   | 0.3   | 2.6  | 1  | 0            |
| 1965                 | Predustyrtye                      | 309   | 10        | 1                             | 1                   | 0.3   | 10.0   | 0  | 1            |
| 1975                 | Aral-region Karakumy              | 303   | 83        | 1                             | 1                   | 0.3   | 1.2  | 0  | 1            |
| 1980                 | Aral-region Karakumy              | 598   | 256       | 1                             | 1                   | 0.2   | 0.4  | 0  | 1            |
| 1980                 | Northern Kyzylkumy                | 598   | 151       | 2                             | 0                   | 0.3   | 1.3  | 1  | 0            |
| 1988                 | Aral-region Karakumy              | 418   | 333       | 11                            | 3                   | 2.6   | 3.3  | 6  | 2            |
| Total for each focus |                                   |   |           |                               |                     |   |  |  |              |
|                      | Aral-region Karakumy              | 2030  | 1031      | 19                            | 8                   | 0.9   | 1.8  | 8  | 7            |
|                      | Predustyrtye                      | 309   | 10        | 1                             | 1                   | 0.3   | 10.0   | 0  | 1            |
|                      | Northern Kyzylkumy                | 1045  | 169       | 5                             | 0                   | 0.5   | 3.0  | 3  | 0            |
|                      | Northern Aral region              | 477   | 145       | 11                            | 0                   | 2.3   | 7.6  | 2  | 0            |
|                      | Trans-Aral region                 | 617   | 89        | 2                             | 2                   | 0.3   | 2.2  | 0  | 2            |
| Totals               |                                   | 3262  | 1444      | 38                            | 11                  | 1.2   | 2.6  | 13   | 10           |

Note: The sum of the third column of 3262 is the number of plague-microbe strains isolated in all of the Northern Aral region over the 10 years examined, and it pertains only to the first part of the table.

Besides 1988, singled out among the other years are 1947, 1962, 1965, and 1980, during which 10, 3, 6, and 3 plague-microbe cultures were isolated from house mice.

On the whole, over all those years, points of finds of plague-infected house mice or their fleas were distributed in the following manner throughout the autonomous foci (see the table): Aral-region Karakumy, 14 (one point each in 1958, 1975, and 1980; three points in 1965; eight points in 1988); northern coastal zone of the Aral Sea, with adjacent regions, 2 (one point each in 1947 and 1965); Northern Kyzylkumy, 3 (two in 1965, and one in 1980); the trans-Aral region, 2 (1950, 1963); Predusturye, 1 (1965).

In terms of the number of plague cultures isolated from the house mouse, first place (48.6 percent) belongs also to the Aral-region Karakumy, and substantially fewer strains of the plague microbe from mice were isolated on the northern coast (29.5 percent) and in the Northern Kyzylkumy.

Such a distribution stems from the fact that the Aral-region Karakumy represents the most active autonomous focus in the Northern Aral region, and that is where, during the years analyzed, almost half of all cultures of plague agent were isolated (48.9 percent); in individual years (1958, 1988), that figure has reached 81-90 percent. Against the backdrop of such a high epizootic activity for the focus, which is often combined with an elevated population level of house mice, those rodents have become infected with plague.

Sick house mice have been caught both in open habitats and in human population centers, and if the number of samples with plague-infected mice is almost identical (10 and 13), the number of infected mice in settlements is a little over twice the number in the field (27 and 11).

Five out of 10 samples of field material with plague-infected mice were taken in the vicinity of population centers (Akabay, Kara-Bugut, and the Komsomol and Engels kolkhozes).

Plague-infected mice in various years have been caught at the Saksaul station (the northern coast, 1947—10 cultures; there were also cases of human illness at this time), at the Chegan Sovkhoz and the Asmangeldy settlement in Northern Kyzylkumy (1962), in the Kulandy settlement (northern coast), at the Voroshilov settlement, 86th siding (Aral-region Karakumy, 1965), and at the Inkar-Darya settlement (Northern Kyzylkumy, 1980). The greatest number of population centers with infected house mice was recorded in 1988—the city of Aralsk, plus the settlements of Amanutkul, Koszhar, Kumbazar, Akbay, and Kumzhiyek. In that same year, positive serological reactions were obtained from mice from Aralsk, Koszhar, and Akbay (in addition to isolated cultures), as well as from Staraya Bungunya and Tokhabay. With the exception of one population center (Urman, Chelkarskiy Rayon), all the centers infected in 1988 are in the northern Aral coast/Karakumy autonomous focus.

Everything that has been said supports the following conclusions:

1. House mice in the Northern Aral region are most often involved in the epizootics of plague in years in which the populations of that species, the great gerbil and, often, other plague-carriers are large and the natural foci of the plague are activated.

2. The largest number of locations of finds of plague-stricken house mice and the large number of infected animals have been noted in the Aral-region Karakumy, the most active autonomous focus of the Northern Aral region.

3. Points with plague-infected mice are recorded with virtually the same frequency in population centers and in the field, but some of the field finds are on the outskirts of population centers. The number of cultures of plague agent isolated from house mice from population centers is more than twice that for mice caught in the field.

4. House mice living outside populations centers, as well as on their outskirts and in outdoor structures, have rather close contact with the burrows of the primary plague-carrier and get ectoparasites from them, thanks to which the plague agent penetrates the mouse population.

5. A large number of plague mice in population centers was recorded only twice—in 1947 (10 specimens) at the Saksaul station, and in 1988 at six population centers (8 specimens). The high infection rate among house mice and their concentration in the Aral-region Karakumy in 1988 were related both to activation of that autonomous focus and to the sharp increase in the population size of the mice. The spread of sick mice throughout the area was probably helped by their being brought in with hay from the epizootic territory.

6. The involvement of the house mouse in the plague epizootics in the Northern Aral region and other regions makes it necessary to conduct systematic monitoring of the population size of that species. Regular, broad-based extermination in population centers, especially rural populations centers, in the Northern Aral region represents a substantial and needed contribution to the prevention of plague in that region.

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- Organization and Improvement of Dermatological-Venereal Disease Care in the Republic**  
927C0477D Alma-Ata ZDRAVOOKHRANENIYE KAZAKHSTANA in Russian No 11, Nov 91 pp 10-12
- [Article by I. R. Tsygankova, O. S. Plotnikova, L. T. Zubkova, M. I. Koshkarova, Scientific Research Skin/Venereal Disease Institute, Alma-Ata; UDC (615.5+616.97):06]
- [Text] The situation in the health care sector in our republic, as in the entire country, is largely determined by the socioeconomic environment and the health and hygiene at work and in the home among the people, who have fully experienced for themselves the left-over principle of financing of this most important sector.
- The program of the Kazakh SSR government associated with the transition to a market track provides, in the realm of health care, that market relations must bear a limited nature and that the state will assume the main part of the burden associated with ensuring the development of health care sector, that is, the main principle of socialist medicine will be preserved: its accessibility to everyone.
- Perestroyka in the work of the skin/venereal disease institutions is proceeding as a result of the development and strengthening of specialized types of treatment; re-outfitting with new types of equipment; the introduction of new methods and means of prevention, diagnosis, and treatment of skin/venereal disease; and a radical improvement of the material base. For example, recent years have seen the opening of the first phase of a hospital at the Scientific Research Skin/Venereal Disease Institute and a 150-bed oblast dispensary building in Karaganda; construction is continuing of a pediatric fungus division (30 beds—in Taldy-Kurgan) as well as a new building for the oblast skin/venereal disease dispensary in Guryev Oblast and the Dzhalgash rayon skin/venereal disease dispensary in Kzyl-Orda Oblast; the

second phase of the clinic of the Scientific Research Skin/Venereal Disease Institute is being raised, as is the Shemonaikha rayon skin/venereal disease dispensary in East Kazakhstan Oblast. Major and running repairs are being done, and possibilities are being explored for new construction (for example, the Alma-Ata oblast skin/venereal disease dispensary). However, the overwhelming majority of our facilities are located in unsanitary conditions, without basic communications. All that is made worse by crowding and congestion. After all, there are 3.0 skin/venereal disease beds per 10,000 population, and 0.5 doctors per 10,000 (the norms are 3.6 and 0.7). The situation is even worse in a number of rural rayons, where vacancies exist from year to year for skin/venereal disease specialists. That pertains, in particular, to six rayons in Karaganda Oblast, five in Kokchetav Oblast, four in Ural Oblast, three in East Kazakhstan Oblast, and two each in Alma-Ata Oblast and Mangistau Oblast.

For Kazakhstan SSR as a whole, recorded cases of syphilis were down 18.1 percent in 1990 from the previous year; gonorrhea was down 0.9 percent. In Karaganda Oblast, however, the number of syphilis cases grew 2.4-fold (to 44 from 26); they grew 3.6-fold in North Kazakhstan Oblast (to 25 from 7); and they grew by 2-4 cases in Alma-Ata and Ural oblasts. The number of gonorrhea cases for that period grew considerably in Taldy-Kurgan Oblast (by 21.9 percent, Kzyl-Orda Oblast (by 23.4 percent), in Tselinograd Oblast (by 12.3 percent), in Alma-Ata Oblast (by 10.6 percent), and in the city of Alma-Ata (by 9.3 percent)— primarily a result of acute forms.

In per 100,000 population figures, syphilis morbidity dropped for the republic as a whole from 1.8 in 1989 to 1.4 in 1990; gonorrhea morbidity dropped from 107.0 to 105.5. However, syphilis morbidity remains higher than the republic level in Karaganda, North Kazakhstan, and Ural oblasts and in Alma-Ata (from 2.7 to 4.1). Gonorrhea morbidity remains high in Alma-Ata and East Kazakhstan oblasts and especially Tselinograd oblast and the city of Alma-Ata, where the figure is almost twice the republic average.

Analysis of data for 1989 showed that most of the individuals with syphilis and gonorrhea are in the age group 20-39 (68.6 percent and 78.1 percent, respectively). Sociological research being conducted and a summary of the literature data for our country and abroad enable the conclusion that an increase in the incidence of sexually transmitted diseases among teenagers is the result of a change in sexual behavior and the practice of using contraceptives, the rapid increase in the teenage population and in urbanization, and an observed tolerance for various kinds of sexual relations that previously were considered unacceptable. Underlying personality formation is an intricate complex of sociopsychological factors that have a pronounced effect on youth under the age of 20: alcoholism among parents and relatives, low educational level, unstable family life, profession, environment, mentally traumatic situations.

Analysis of outpatient charts for eight regions of the republic for 1989 and the first half of 1990 for teenagers with venereal disease showed that in most cases they were drinking alcohol when they became infected and that their sex lives began early. In addition, what comes to the fore is that teenagers create multicontact foci of infection. In Karaganda, for example, a multicontact focus was recorded whose source was a 15-year-old female student of a night school. The parents had divorced eight years earlier, and the child was raised by the mother. There was a younger brother in the family. The girl had been using alcohol for a year, and she had been drinking when she had her first sexual contact. At present, she has casual sex with people she barely knows. Examination revealed chronic gonorrhea. The following month, she had eight sex partners. Four of them turned out to have gonorrheal urethritis.

To prevent the growth of venereal disease among teenagers, joint seminars of medical personnel and teachers from schools, academies and higher institutes of education are being held in various regions of Kazakhstan. The oblast skin/venereal disease dispensaries are staying in constant touch with internal affairs officials, district police, and workers of children's and special centers. In Karaganda, with a department of the medical institute programs involving venereal disease are being developed for youth; also being developed are differentiated health-education techniques for individual contingents of teenagers.

In 1990, 71.9 percent of individuals with syphilis in the republic were actively identified, and 54.3 percent of those with gonorrhea. The sources of infection were found in 56.9 percent and 47.5 percent, respectively. Some 17 percent of the individuals who were identified last year as having syphilis were identified with the Wassermann test in somatic hospitals, among pregnant women and blood donors. In addition, in Kazakhstan, the introduction of microtests for the rapid diagnosis of syphilis, an unacceptable reduction is noted in the formulation of classical specific reactions (Wassermann, RIT [treponema immobilization reaction], FTA-ABS).

The unfavorable epidemiological situation that has come about in recent years regarding scabies morbidity in a number of regions of the republic is cause for concern. In 1990, for example, the number of scabies patients grew 1.5-fold over the number for 1989 in Guryev and Dzhezkazgan oblasts, by 5.3 percent in Kustanay Oblast, and more than fourfold in Leninsk, in Kzyl-Orda Oblast.

Analysis of the causes of the growth of that infection demonstrated that it is the result of the spread of scabies among attached pediatric, school, and student collectives (nearly 60 percent of the entire number of patients). As a rule, in foci, children, university students, and technicum and trade-school students returning from the holidays often are not examined by medical personnel, whereas cases of the infection have already been recorded in their families.



Extremely unsatisfactory is the material-technical base of the overwhelming majority of boarding schools and dormitories, where it is so crowded that 2-3 children are placed in one bed. There are no decontamination centers, shower facilities, disinfecting equipment. In some oblast centers (Aktyubinsk and Kokchetav), there's only one bath in operation. The diagnosis of scabies, which is often taken to be dermatitis, an allergy, or something else, suffers. As a result, under the supervision of medical personnel and receiving no medical treatment, the patients continue to infect those around them.

The situation is not good with dermatomycosis, the number of cases of which grew by 6.1 percent from 1989 to 1990 for the republic as a whole, by 1.7-fold in Chimkent and Ural oblasts, by 27.6 percent in Aktyubinsk Oblast, and by 10-17 percent in North and East Kazakhstan oblasts and Guryev and Dzhambul oblasts. Both trichophytosis and microsporia are also growing (4.4 percent and 6.9 percent).

A good many unresolved problems and difficulties in health education have cropped up. An analysis performed by the USSR Ministry of Health All-Union Scientific Research Center for Prophylactic Medicine showed that the overwhelming majority of medical workers, not having a procedure for the systematic analysis and comprehensive evaluation of the problems of health care, look upon health education too simplistically, performing it only episodically and not linking that to causes and conditions that generate a given problem in health care. As a result, a broad segment of the medical community has a negative, skeptical opinion of health education.

In October 1988, an order was issued by the USSR Ministry of Health, No 770: "On the improvement of hygiene education among the population and information about healthy lifestyles." It called for a radical restructuring of hygiene education, especially among the generation coming up, and a standardized policy regarding primary prophylaxis aimed at preventing disease and strength the health of the population.

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### A Family Source of HIV Infection

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[Text] The first case of AIDS in our country was recorded in 1987<sup>1,3</sup>, but as of December 1989 more than 500 persons were found to be infected by the human immunodeficiency virus (HIV). Twenty-four of the HIV-infected persons were diagnosed as having AIDS, and 14 persons of that group died<sup>9</sup>. A regularly scheduled testing for AIDS among various segments of the population was undertaken in the USSR in 1987. Examinations were primarily made of foreign students who had arrived in the USSR from countries with significant levels of AIDS infections<sup>1,5</sup>. During the years 1988-1989 there was an increase in the number of infections among inhabitants of our country. Thus, 11 foreign citizens were diagnosed to have HIV infections in Leningrad, and there was only one female native Russian who was found to have contracted the infection through sexual relations with Africans. In 1988 the number of infected residents of the city was double that of the foreign citizens. An analysis of the epidemic situation<sup>6</sup> offers grounds to assume that HIV infections are being spread among the population by every possible mode, i.e., through sexual contact, parenterally, and from mother to fetus, although we do not yet know when this mode of transmission began.

The first case of an HIV infection in a citizen of the USSR is believed to have occurred in 1982 and was brought here from Tanzania. Infection took place as a result of a homosexual contact with a Tanzanian resident. Following his return to the USSR, the afflicted person remained a source of infection until 1987 when his illness was diagnosed for the first time.

We are currently observing a family in which the source of infection was a woman who was infected in the USSR, possibly during the period of 1977-1978.

This female resident G. of the city of Leningrad was born in 1960. She gave blood for the first time as an unpaid donor on 10 Feb 1988 and was tested for HIV infection. The results of the immunoenzyme analysis (ELISA) proved positive, and the immune blot test disclosed antibodies to viral proteins having a molecular mass of 160, 120, 41, 66, 55, 31, 24, and 17 kD which were indicative of an HIV infection. We established that between 1977 and 1979 G. had sexual contacts with Africans from Somalia and the Congo as well as with a citizen of Syria.

In 1982 G. married a citizen of the USSR to whom she remained married until 1985. In 1982 G. gave birth to a girl. The pregnancy and birth proceeded without complications. In 1985 a resident of Cuba was a sexual partner of G. for a brief period of time.

In May 1987 she married for the second time to F., born in 1962. The patient has noticed chronic hyperacidic gastritis as a result of endured illnesses. In 1978 genital and oral-facial herpes infections appeared for the first time that subsequently became chronic with recurrences every three to six months. She considered herself to be virtually healthy and did not see any physicians. An examination disclosed mobile elastic cervical lymphatic

nodes of all groups having a diameter of 0.7 - 0.8 cm, axillary nodes 0.5 cm in diameter. A moderate bilateral increase in the salivary glands was observed along with herpes elements on the mucous membrane of the oral cavity and the skin of the left hand. The liver protruded 1 cm out from the rib arch.

Blood analysis: Hb 112 g/l, rbc  $4.0 \times 10^{12}/l$ , wbc  $4.0 \times 10^9/l$ , p. 1 percent, s. 50 percent, e. 3.1 percent, lymph. 41 percent, mon. 1 percent; ESR 35 mm/h. Total protein 32.3 g/l, albumins 47.8 percent, globulins:  $\alpha_1$  3.8 percent,  $\alpha_2$  7.6 percent,  $\beta$  10.7 percent,  $\gamma$  30.0 percent. Functional

liver tests without deviations from the norm, HBsAg not detected. Herpes simplex virus antigen detected in scrapings from skin and mucous membrane lesion sites. Increased antibody titer to cytomegalovirus (CMV) observed. Immunological indices were significantly lowered: CD4<sub>cl</sub> 31.3 percent, CD8<sub>cl</sub> 38.6 percent, CD4/CD8 0.81. Diagnosis: HIV infection. AIDS-related complex, recurrent disseminated herpes simplex, dermal-mucal erosive form, acquired cytomegaloviral infection, sialadenitis (or IIIA stage of secondary illnesses as classified by V.I. Pokrovskiy, 1989).

Dynamics of T-cell Immunity Indices in HIV-Infected Family Members

| HIV-Infected Family Members | Date of Observation | Immunological Indices                   |      |   |      |         |
|-----------------------------|---------------------|---|------|---|------|---------|
|                             |                     | CD4                                     |      | CD8                                     |      | CD4/CD8 |
|                             |                     | abs. number of cells in $1\text{ mm}^3$ | %    | abs. number of cells in $1\text{ mm}^3$ | %    |         |
| G. (mother)                 | 16.02.88            | 410                                     | 31.3 | 506                                     | 38.6 | 0.81    |
|                             | 13.05.88            | 315                                     | 24.0 | 525                                     | 40.0 | 0.80    |
|                             | 11.10.88            | 186                                     | 17.5 | 321                                     | 30.0 | 0.58    |
|                             | 21.02.89            | 380                                     | 34.0 | 597                                     | 53.0 | 0.64    |
|                             | 11.06.89            | 303                                     | 24.0 | 620                                     | 49.0 | 0.49    |
|                             | 18.07.89            | 340                                     | 34.0 | 480                                     | 48.0 | 0.75    |
|                             | 17.10.89            | 520                                     | 40.0 | 520                                     | 40.0 | 1.0     |
|                             | 09.01.90            | 300                                     | 30.0 | 330                                     | 33.0 | 0.90    |
|                             | 01.03.88            | 600                                     | 28.0 | 652                                     | 30.3 | 0.92    |
| Yu.(daughter)               | 13.05.88            | 610                                     | 31.6 | 717                                     | 37.0 | 0.85    |
|                             | 11.10.88            | 330                                     | 15.0 | 702                                     | 31.6 | 0.47    |
|                             | 24.02.89            | 424                                     | 24.0 | 831                                     | 47.2 | 0.51    |
|                             | 26.05.89            | 703                                     | 36.0 | 777                                     | 38.3 | 0.94    |
|                             | 18.07.89            | 630                                     | 42.0 | 660                                     | 44.0 | 0.95    |
|                             | 11.12.89            | 800                                     | 36.0 | 800                                     | 36.0 | 1.0     |
|                             | 16.02.88            | 840                                     | 38.7 | 700                                     | 32.3 | 1.2     |
| F.(husband)                 | 27.08.89            | 800                                     | 36.3 | 667                                     | 30.0 | 1.21    |
|                             | 09.01.90            | 600                                     | 40.0 | 711                                     | 48.0 | 0.83    |

Symptoms of nervous system injury subsequently intensified. These included lassitude, indisposition, drowsiness, and recurrences of oral-facial and genital herpes became more frequent. Episodes of tracheobronchitis began to recur at intervals of one month, accompanied by fever, and toxic effects. The last episode was of mycoplasmic etiology. In view of the deteriorating situation and the continuing drop in the T-cell immunity indices (the number of CD4<sub>cl</sub> fell to 186 per  $1\text{ mm}^3$ , 7.5 percent; CD4/CD8 0.58; see table), we prescribed retrovir at a dose of 250 mg three times daily, and zovirax at a dose of 1000 mg daily during the period of herpes recurrences. The retrovir yielded a clinical effect and immunological indices improved. However, on 08.08.89 pains appeared in the right iliac region in a background of specific therapy. They were considered to be a complication of a hepatic diagnostic puncture. The persistently growing pains were considered an indication for a

laparotomy which disclosed a phlegmonic appendicitis and mesadenitis. Cultures from the appendix exhibited a gram-positive flora of Citrobacter.

The blood analysis prior to the operation offered no grounds for suspecting a suppurative infection of the abdominal cavity (wbc  $3.5 \times 10^9/l$ , p. 7 percent, s. 58 percent, e. 1 percent, lymph. 34 percent, mon. 3 percent, ESR 22 mm/h). The appendectomy proceeded successfully. Retrovir and broad-spectrum antibiotics were prescribed during the post-operative period. Repeated bacterial infections and continuously recurring herpes in a background of disrupted immunity were indicative of a progressive HIV infection and transition to the AIDS stage. Retrovir and zovirax therapy allow for the maintenance of a subcompensated condition.

All the family members of G., daughter, mother, and both husbands were contacted and examined.



The daughter of G. from her first marriage<sup>7</sup> has been constantly ill since her first days of life. During the daughter's early neonatal period there was an enlargement of the salivary glands, reduced salivation, and at the age of one month she developed otitis which became chronic with frequent exacerbations. At the age of 1.5 months she was afflicted with bilateral croupous pneumonia. Since the age of two years she has had monthly acute respiratory infections, a constant sub febrile temperature, reduced appetite, and loose stools. During this period iron-deficient anemia was detected. At the age of two years she suffered a severe case of chicken pox after which she twice was afflicted with shingles. Since the age of two she was observed to be suffering from persistent generalized lymphadenopathy. An inspection of her fingers disclosed herpes rashes. There was pigmentation following herpes zoster on the skin of the right fifth intercostal area of the thoracic cage. Dense enlarged salivary glands were palpated bilaterally as well as anterior-posterior cervical, axillary, inguinal lymph nodes that were elastic and mobile having a diameter of 0.5 cm. The liver was 1.5 cm lower than the rib margin and the spleen was enlarged. Moderate anemia (Hb 110 g/l), leukopenia ( $3.9 \times 10^9/l$ ), insignificant  $\gamma$ -globulinemia (21.6 percent). Salivary deposits exhibited cytomegaloviral cells and an increased antibody titer to the cytomegalovirus.

An immunoenzyme and immune blot test (antibodies to HIV proteins with a molecular weight of 18, 24, 31, 41, 51, 55, and 160 kD) confirmed the diagnosis that had been proposed solely on the basis of epidemiological and clinical data: HIV-infection and AIDS-related complex (stage IIIb of secondary diseases). The immunological indices are presented in the table. Following the administration of azidothymidine at a dose of 200 mg daily there was a decrease in the feeling of indisposition and lassitude. Appetite improved, and the size of lymph nodes significantly decreased. The CD4/CD8 ratio increased from 0.51 to 1.0.

F. who was married to G. since 1987 was tested for HIV infection in February 1988 and was found to be serum negative. He considered himself to be sound and had no complaints about his health. However, the diameter of the cervical and axillary lymph nodes was up to 0.5 cm. On July 13 he was operated on for a suppurative infected coccyx. On July 16 his temperature rose to 38.6°C and he felt pains in his muscles and joints, experienced nausea and vomited once. He was hospitalized at an infectious disease station on the fifth day of his illness with a suspicion of pseudo tuberculosis. At the station a maculopapulous rash was found on his face and torso along with enlarged submaxillary, posterior lymph nodes up to 0.7 - 1.0 cm. The liver protruded by 1.5 cm out from the rig margin. On the seventh day aphthae appeared on the buccal mucous membrane. The elements of the rash remained for 1 day. Fever and toxic effects persisted for seven days. Lymphadenopathy and hepatomegaly were retained. Blood analysis: Hb 160 g/l, rbc  $5.1 \times 10^{12}$  g/l, wbc  $2.8 \times 10^9/l$ , p. 7 percent, s. 40 percent, b. 1 percent,

lymph. 49 percent, mon. 3 percent; ESR 33 mm/h. Serological and bacteriological tests for pseudo tuberculosis and the ELISA with HIV antigen on July 21 and 22 were negative. A serum conversion took place in the course of the next hospital examination on 21 Oct 1988. Diagnosis: HIV infection, stage of persistent generalized lymphadenopathy. The diagnosis was confirmed by ELISA and immune blot (antibodies to viral proteins with mol. wt. of 160, 41, 17, 24, 31, 55 kD). The immunological indices are presented in the table. Subsequently F. began to be disturbed by a recurrent dermal-mucous erosive genital and orofacial herpes. A mycotic lesion of the heel skin appeared along with an acne-like folliculitis. The CD4/CD8 ratio fell from 1.2 to 0.9. This offered grounds for altering the stage of the HIV infection and making a diagnosis of AIDS-related complex (IIIA stage of secondary diseases).

In addition to the daughter and husband, the mother and first husband of patient G are also registered at the clinic. They are undergoing serological tests for HIV infection once every three months and so far are serum negative. The absence of any infection in the grandmother who has been caring for the sick child for seven years confirms the view that this infection cannot be transmitted by ordinary everyday contact<sup>20</sup>.

We do not have any reliable data on the actual date the woman was infected, but in view of the daughter's vertical mode of infection, we can assume that this occurred no later than 1981. A retrospective study of the epidemiological history allows us to conclude that infection took place at an earlier date, i.e., in 1977 or 1978. The source of the infection could be the woman's sexual partner from the Congo, a country in which there were 1250 AIDS patients by the end of 1987. One cannot exclude the citizen of Somalia as a possible source of the infection. Data on AIDS patients in this country reached us as late as 1989. On July 31 we received a report about four cases of the disease. The first cases of AIDS in Africa were recorded in 1984, but examinations of blood sera have demonstrated that the infection has been prevalent there since the 1950's<sup>2, 12, 14, 17, 18</sup>. Consequently, Africans from the Congo and Somalia in 1977 - 1978 could have been infected. The time of the woman's infection is indirectly confirmed by the appearance of a genital herpes in 1978 that constituted an AIDS-related disease transmitted by sexual means. Such a prolonged period of serum positive readings in the patients we observed does not contradict the literature data according to which antibodies to the virus are assayed four to fifteen years (seven to eight years on the average) after infection<sup>8, 15, 19</sup>.

Whereas the source and time of the mother's infection remain debatable, there is no doubt that her daughter was infected by the vertical mode in 1982. Some believe that in contrast to adults, HIV infections in children follow a malignant course and the clinical manifestations of AIDS appear during the first 24 - 34 months of life<sup>15, 19</sup>. Thus, S. Blanche<sup>10</sup> observed 28 infected children over a course of 10 months. Of that group the condition in

nine was grave and five died. The author believes that the survival of 60 percent of children infected intrauterinely is five years, and for 30 percent the survival time is no more than two years.

Our observation indicates that the longevity of children afflicted with AIDS might be significantly longer inasmuch as the little girl is now seven years old. The child's compensatory condition which might be attributed to adequate etiologic therapy and the treatment of recurrent diseases suggests that she may attend school. Our examination of children who attend schools together with HIV-serum positive and AIDS-afflicted children of the same age has demonstrated that contacts between pupils do not lead to infection. However, the scientific literature lacks information about the susceptibility of an HIV-infected child to conventional children's diseases such as streptococcal tonsillitis, measles, mycoplasmosis, respiratory infections, and others which could become critical in a background of immunodepression. Permission to attend school may be based on social and psychological criteria with due attention to the stage of HIV infection and the results of immunological examinations.

The source of infection which we described is also noteworthy in that the observed family members exhibited a natural course of the infection process. Thus, during the two-year period of the mother's hospitalization the HIV-infection passed to the AIDS stage and that of the daughter proceeded to the AIDS-related complex. However, particular attention should be given to the husband's infection which occurred via the sexual mode. Most investigators<sup>11, 13, 16, 19</sup> believe that the incubation period following infection is two to three months. This is followed by an acute HIV-infection clinically similar to acute respiratory viral infections and infectious mononucleosis and is frequently accompanied by polyadenopathy, splenic, hepatomegaly, aphthous stomatitis, maculo-papulous rash, and sometimes serous meningitis. Atypical mononuclears show up in the hemograms of 75 percent of the patients which hinders differentiating this disease from infectious mononucleosis. Recovery takes place after two to six weeks during which period serum conversion takes place. The HIV-infection in one patient we observed followed a somewhat unusual course which was similar to pseudo tuberculosis. At the end of the first week the ELISA test was negative. Antibodies to HIV were detected in the ELISA and immune blot tests upon a repeated examination 13 weeks later. Consequently, serological tests for HIV infections should be undertaken during the second and sixth weeks and three months after the onset of the disease in persons exhibiting an unfavorable epidemiological history.

Thus, our observations have documented the appearance of an HIV-infection in a woman infected by a foreigner via heterosexual contact within the territory of the USSR beginning in 1981, and possibly starting in the period 1977 - 1978. A precise diagnosis of AIDS was made in 1989. The HIV infection in the daughter, infected in utero, followed a prolonged (seven years) subcompensated course. Antibodies to HIV were not identified in the patient's second husband during the manifestation of the acute HIV infection, but

were detected 13 weeks later in the ELISA immune blot tests. The grandmother who was in close contact with her granddaughter and her mother remains serum negative after two years of observation.

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### Immunometabolic Criteria of the Differential Diagnosis of False Seropositive and HIV-Infected Individuals

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[Text] After the role of the human immunodeficiency virus (HIV) in the etiology of acquired immune deficiency syndrome (AIDS) was proven,<sup>10</sup> the search began for the optimal methods for detecting in the body of an infected individual the virus-specific antibodies or the virus itself.<sup>8,9</sup>

Each of the screening, reference (enzyme immunoassay, EIA), or expert (immunoblotting) methods for testing the

blood serum of an individual may produce a small number of false-positive, doubtful, or false-negative results.

The social significance of false seropositive results is great and will grow in the coming years in connection with the need to conduct massive screening tests of various groups of the population. A number of researchers<sup>1,3,4</sup> estimate the probability of the appearance of false seropositive results in the various EIA test systems to be 0.001-6.8 percent, including variations even in test systems produced by the same manufacturer.<sup>5</sup> At present, a result is considered seropositive in EIA if two out of two or two out of three analyses indicate HIV antibodies in the individual.<sup>5-7</sup>

In our four-year study, the percentage of seropositive results with EIA—according to data involving two or three verifications with diagnostic test systems of a different manufacturer—ranged from 0.90 percent to 1.92 percent, with an average of 1.49 percent (685 individuals out of 45,938; see Table 1). With expert testing of the seropositive sera in immunoblotting (Table 2), the true HIV infection rate was found to be, on average, 10.66 percent (73 out of 685), with most of the cases among foreign citizens.

Table 1. Volume and Information Value of EIA Testing of Blood Sera

| Test contingent           | Number of individuals tested |        |        |        | Seropositive |         |       |         |      |         |      |         |
|---------------------------|------------------------------|--------|--------|--------|--------------|---------|-------|---------|------|---------|------|---------|
|                           | 1987                         | 1988   | 1989   | 1990   | 1987         |         | 1988  |         | 1989 |         | 1990 |         |
|                           |                              |        |        |        | abs.         | percent | abs.  | percent | abs. | percent | abs. | percent |
| USSR citizens             |                              |        |        |        |              |         |       |         |      |         |      |         |
| In all                    | 4,000                        | 13,289 | 11,059 | 16,436 | 31           | 0.77    | 164   | 1.23    | 201  | 1.82    | 234  | 1.43    |
| from clinical indications | 632                          | 793    | 2,806  | 6,783  | 14           | 2.21    | 47    | 4.40    | 74   | 2.64    | 85   | 1.25    |
| from donors               | 3,368                        | 12,496 | 8,090  | 9,333  | 17           | 0.50    | 117   | 0.94    | 26   | 0.32    | 22   | 0.24    |
| from expert tests         | -                            | -      | 163    | 320    | -            | -       | -     | -       | 101  | 61.96   | 127  | 39.69   |
| Foreigners                | 220                          | 680    | 90     | 164    | 7            | 3.18    | 23    | 10.46   | 13   | 14.44   | 12   | 18.91   |
| Totals                    | 4,220                        | 13,969 | 11,149 | 16,600 | 38           | 0.90187 | 1,272 | 4       | 1.92 | 246     | 1.48 |         |

Table 2. Volume and Information Value of Immunoblotting of EIA-Seropositive Blood Sera

| Test contingent | Number of individuals tested |      |      |      | HIV-infected individuals |         |      |         |      |         |      |         |
|-----------------|------------------------------|------|------|------|--------------------------|---------|------|---------|------|---------|------|---------|
|                 | 1987                         | 1988 | 1989 | 1990 | 1987                     |         | 1988 |         | 1989 |         | 1990 |         |
|                 |                              |      |      |      | abs.                     | percent | abs. | percent | abs. | percent | abs. | percent |
| USSR citizens   | 31                           | 164  | 201  | 234  | -                        | -       | 2    | 1.22    | 16   | 7.96    | 24   | 10.25   |
| Foreigners      | 7                            | 23   | 13   | 12   | 2                        | 28.57   | 7    | 30.43   | 13   | 100.00  | 9    | 75.00   |
| Totals          | 38                           | 187  | 214  | 246  | 2                        | 5.26    | 9    | 1.07    | 29   | 14.02   | 33   | 13.46   |

Attracting interest for the evaluation of the immune status of seropositive individuals is an immunometabolic monitoring system that was first developed in 1989 at the Scientific Research Medical Department of the Expert Diagnosis of AIDS (V. L. Pastushenkov and Yu.

A. Mitin) and that makes it possible to identify a given equivalent of truly HIV-infected individuals.<sup>2</sup> The system includes about 40 indicators of cellular and humoral immunity, nonspecific resistance, and activity of key enzymes of lymphocytes (Table 3).

Table 3. Immunometabolic Map

|  |                  |            |
|--|------------------|------------|
| Date of arrival of sample                |                  |            |
| Treatment facility                       |                  |            |
| Patient                                  |                  |            |
|  |                  | Normal     |
| Leukocytes                               | abs.             | 4.3-9.0    |
| Lymphocytes                              | %                | 23-45      |
|  | abs.             | 1.5-2.4    |
| T lymphocytes (T <sub>3</sub> )          | %                | 41-70      |
|  | abs.             | 0.7-1.4    |
| T helpers (T <sub>4</sub> )              | %                | 23-48      |
|  | abs.             | 0.45-0.85  |
| T suppressors (T <sub>8</sub> )          | %                | 17-25      |
|  | abs.             | 0.27-0.54  |
| Index: T <sub>4</sub> /T <sub>8</sub>    |                  | 1.10-2.20  |
| MIF with PHA                             |                  | 40-75%     |
| MIF with ConA                            | %                | 20-60%     |
| MIF with thymalin                        |                  | -          |
| B lymphocytes (total)                    | %                | 8-19       |
|  | abs.             | 0.19-0.38  |
| B lymphocytes (IgM+)                     | %                | 3-10       |
|  | abs.             | 0.07-1.17  |
| B lymphocytes (IgG+)                     | %                | 2-6        |
|  | abs.             | 0.04-0.11  |
| B lymphocytes (IgA+)                     | %                | 1-3        |
|  | abs.             | 0.02-0.06  |
| IgM                                      | g/l              | 0.65-1.65  |
| IgG                                      | g/l              | 7.5-15.4   |
| IgA                                      | g/l              | 1.25-2.5   |
| IgD                                      | g/l              | 0.003-0.07 |
| IgE                                      | m.e.             | 30-90      |
| C3 component                             | g/l              | 0.6-1.1    |
| Orosomucoids                             | g/l              | 0.55-1.4   |
| Transferrin                              | g/l              | 0.2-3-4.0  |
| α <sub>1</sub> -antitrypsin              | g/l              | 2.0-4.0    |
| α <sub>2</sub> -macroglobulin            | g/l              | 1.5-3.5    |
| Circulating immune complexes, %          |                  | 90-95      |
| IgM in circulating immune complexes, g/l |                  | -          |
| IgG in circulating immune complexes, g/l |                  | -          |
| Enzyme activity in lymphocytes           |                  |            |
| SDH                                      | extinction units | 0.070-0.10 |
| LDH                                      | extinction units | 0.270-0.34 |

Table 3. Immunometabolic Map (Continued)

|                                |                  |            |
|--------------------------------|------------------|------------|
| G-6-PDH                        | extinction units | 0.136-0.24 |
| $\alpha$ -GPDH in cytoplasm    | extinction units | 0.217-0.30 |
| $\alpha$ -GPDH in mitochondria | extinction units | 0.191-0.22 |
| NAD-oxidases                   | extinction units | 0.090-0.12 |
| NADP-oxidases                  | extinction units | 0.080-0.12 |
| MDH cytoplasmic                | extinction units | 0.100-0.15 |
| MDH mitochondrial              | extinction units | 0.070-0.10 |
| NBT test baseline              | extinction units | 0.090-0.12 |
| NBT test stimulated            | extinction units | 0.150-0.22 |
| LCB test                       | standard units   | 1.5-1.7    |

We shall submit the results of immunometabolic monitoring that we conducted for 73 false seropositive (in EIA) individuals and 20 HIV-infected individuals. The monitoring included a study of the following indicators of the immune system: T lymphocytes ( $T_3$ ), T helpers ( $T_4$ ), T suppressors ( $T_8$ ) on an Epix-C flow-through cytometer with monoclonal antibodies provided by Ortho Diagnostic Systems (United States); functional activity of lymphocytes in the leukocyte migration inhibition test with ConA (5  $\mu$ g/ml) and PHA (20  $\mu$ g/ml); B lymphocytes bearing IgM, IgA, IgG; serum levels of immunoglobulins (M, G, A, D), C3 component complement, and other acute-phase proteins of blood serum (orosomucoid, transferrin,  $\alpha_1$ -antitrypsin,  $\alpha_2$ -macroglobulin) by means of radial immunodiffusion; level of protection by cellular factors of nonspecific

resistance in lysosomal-cation test and NBT test by photometric method of our own modification.<sup>2</sup>

We judged the metabolism of immunocompetent cells from the activity of key enzymes of the basic metabolic cycles: lactate dehydrogenase (LDH),  $\alpha$ -glycerophosphate dehydrogenase ( $\alpha$ -GPDH) in two isoforms (cytoplasmic and mitochondrial), glucoso-6-phosphate dehydrogenase (G-6-PDH), succinate dehydrogenase (SDH), malate dehydrogenase (MDH) in two isoforms, and NAD- and NADP-oxidases determined photometrically.

Our studies established that the HIV-infected group exhibited a tendency toward decline in absolute number of  $T_4$ , index of differentiation ( $T_4/T_8$ ), and functional activity of lymphocytes and a statistically reliable ( $p$ ) increase in number of  $T_8$  lymphocytes (Table 4).

Table 4. Characteristics of T Lymphocytes and Their Subpopulations in False Positives and HIV-Infected Individuals ( $M \pm m$ )

| Test Group      | Lymphocytes    |                | $T_3$           |                 | $T_4$           |                | $T_8$           |                 | $T_4/T_8$       | MIF PHA           | MIF ConA          |
|-----------------|----------------|----------------|-----------------|-----------------|-----------------|----------------|-----------------|-----------------|-----------------|-------------------|-------------------|
|                 | abs.           | %              | abs.            | %               | abs.            | %              | abs.            | %               |                 |                   |                   |
| False positives | 2.4 $\pm$ 0.25 | 34.3 $\pm$ 3.8 | 1.47 $\pm$ 0.20 | 64.4 $\pm$ 4.2  | 0.86 $\pm$ 0.13 | 36.9 $\pm$ 2.6 | 0.72 $\pm$ 0.14 | 30.4 $\pm$ 3.5  | 1.41 $\pm$ 0.16 | 78.0 $\pm$ 8.6    | 69.3 $\pm$ 7.8    |
| Infected        | 1.9 $\pm$ 0.22 | 30.3 $\pm$ 3.3 | 1.35 $\pm$ 0.26 | 60.8 $\pm$ 11.9 | 0.68 $\pm$ 0.14 | 34.2 $\pm$ 4.8 | 1.06 $\pm$ 0.2  | 49.7 $\pm$ 7.9* | 0.94 $\pm$ 0.28 | 97.25 $\pm$ 11.67 | 100.75 $\pm$ 14.9 |

\*— $p$ ) individuals is 73; the number of infected individuals, 20.

With the exception of B lymphocytes (IgA), no substantial differences were identified in number of B lymphocytes and their subpopulations, in the serum

levels of the four basic classes of immunoglobulins, or in the level of circulating immune complexes (tables 5 and 6).

Table 5. Characteristics of B Lymphocytes and Their Subpopulations in False Positives and HIV-Infected Individuals

| Test group      | B (total)       |                | B (IgM)         |                | B (IgG)         |               | B (IgA)         |               |
|-----------------|-----------------|----------------|-----------------|----------------|-----------------|---------------|-----------------|---------------|
|                 | abs.            | %              | abs.            | %              | abs.            | %             | abs.            | %             |
| False positives | 0.43 $\pm$ 0.12 | 16.3 $\pm$ 1.5 | 0.12 $\pm$ 0.03 | 5.6 $\pm$ 0.7  | 0.17 $\pm$ 0.03 | 7.2 $\pm$ 1.2 | 7.71 $\pm$ 0.02 | 3.4 $\pm$ 0.6 |
| Infected        | 0.3 $\pm$ 0.02  | 15.1 $\pm$ 2.8 | 0.07 $\pm$ 0.01 | 4.14 $\pm$ 0.7 | 0.14 $\pm$ 0.08 | 7.0 $\pm$ 1.6 | 6.9 $\pm$ 0.13* | 3.4 $\pm$ 0.9 |

Note: here and in Table 7, the asterisk (\*) signifies— $p$

**Table 6. Characteristics of Immunoglobulins of Blood Serum and Circulating Immune Complexes in False Positives and HIV-Infected Individuals (*M* +/- *m*)**

| Test groups     | Immunoglobulin, g/l |                |               |                | Circulating immune complexes, % |
|-----------------|---------------------|----------------|---------------|----------------|---------------------------------|
|                 | IgM                 | IgG            | IgA           | IgD            |                                 |
| False positives | 1.12 +/- 0.4        | 12.36 +/- 0.69 | 1.66 +/- 0.2  | 0.339 +/- 0.09 | 89.84 +/- 2.0                   |
| Infected        | 1.2 +/- 0.25        | 11.7 +/- 1.7   | 2.24 +/- 0.35 | 0.338 +/- 0.07 | 87.3 +/- 2.9                    |

Study of the indices of nonspecific resistance revealed an increase in the activity of cell factors. An increase was noted in the activity of oxygen-dependent bactericidal systems of neutrophils. The level of stimulated activity in the NBT test in individuals infected with HIV exceeded that index in false seropositive individuals by almost twofold ( $p > 0.001$ ). At the same time,

a decline was noted in the activity of LCP [lysosomal cation protein], which reflects the oxygen-independent path of the bactericidal activity of neutrophils, in the group of HIV-infected individuals. No statistically significant differences were found in the study factors of humoral immunity and content of acute-phase serum proteins (Table 7).

**Table 7. Factors of Nonspecific Resistance and Acute-Phase Serum Proteins in False Positives and HIV-Infected Individuals (*M* +/- *m*)**

| Test groups     | NBT test, extinction units |                 | LCB, arbitrary units | Indicator, g/l |                 |               |                           |                         |
|-----------------|----------------------------|-----------------|----------------------|----------------|-----------------|---------------|---------------------------|-------------------------|
|                 | baseline                   | stimulated      |                      | C3 complement  | orosomucoid     | transferrin   | $\alpha_2$ -macroglobulin | $\alpha_1$ -antitrypsin |
| False positives | 0.109 +/- 0.02             | 0.161 +/- 0.02  | 1.4 +/- 0.04         | 0.605 +/- 0.07 | 0.494 +/- 0.05  | 2.58 +/- 0.24 | 1.54 +/- 0.23             | 3.23 +/- 0.69           |
| Infected        | 0.125 +/- 0.02             | 0.324 +/- 0.18* | 1.29 +/- 0.05        | 0.588 +/- 0.09 | 0.624 +/- 0.127 | 2.87 +/- 0.37 | 2.107 +/- 0.78            | 4.127 +/- 0.658         |

Determination of the activity of the enzymes in blood lymphocytes showed that in the HIV-infected group, there was a reduction in the LDH activity

and the mitochondrial form of MDH, plus an increase in SDH activity and especially G-6-PDH (Table 8).

**Table 8. Activity of Enzymes in Lymphocytes of False Positives and HIV-Infected Individuals (*M* +/- *m*)**

| Test group      | Indicator, extinction units |                |                |                             |                                |                |                |                 |                   |
|-----------------|-----------------------------|----------------|----------------|-----------------------------|--------------------------------|----------------|----------------|-----------------|-------------------|
|                 | SDH                         | LDH            | G-6-PDH        | $\alpha$ -GPDH in cytoplasm | $\alpha$ -GPDH in mitochondria | NAD-oxidases   | NADP-oxidases  | MDH cytoplasmic | MDH mitochondrial |
| False positives | 0.146 +/- 0.04              | 0.216 +/- 0.03 | 0.221 +/- 0.04 | 0.251 +/- 0.05              | 0.194 +/- 0.05                 | 0.148 +/- 0.02 | 0.160 +/- 0.07 | 0.162 +/- 0.05  | 0.173 +/- 0.06    |
| Infected        | 0.184 +/- 0.06              | 0.152 +/- 0.02 | 0.351 +/- 0.10 | 0.253 +/- 0.08              | 0.196 +/- 0.07                 | 0.150 +/- 0.03 | 0.09 +/- 0.008 | 0.145 +/- 0.05  | 0.108 +/- 0.03    |

Thus, unlike false seropositives, HIV-infected individuals show an inversion of the index of differentiation of T lymphocytes ( $T_4/T_8$ ) and a decline in functional indices of the immune system. Against the backdrop of a decline in the immune response, some factors of nonspecific resistance are amplified, particularly the oxygen-dependent bactericidal activity of phagocytic cells; LDH and MDH activity declines, and G-6-PDH and SDH activity increase.

The immunometabolic monitoring system proposed here can be used for searching out differential-diagnosis criteria, as well as in other immunodeficient states.

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### Diagnosis of HIV-Induced Infections With EIA Techniques in USSR

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[Text] For the diagnosis of HIV-induced infection, techniques are used that enable identification of antibodies to various proteins of the virus, viral antigens, and nucleic acids, as well as isolation of the virus.

The main technique for the diagnosis in the USSR as well as in the rest of the world is enzyme immunoassay (EIA), which enables determination of antibodies in blood plasma and in blood serum. Determination of viral antigens in plasma and serum does not have much diagnostic importance, because the antigens are, more often than not, blocked by the antibodies and are found in very few cases.

Current world practice in diagnosing HIV infection includes two stages of testing. The first stage consists in determining serum or plasma antibodies as compared with total viral antigens with solid-phase EIA. The second stage consists in determining antibodies to specific proteins of the virus by means of immunoblotting.

The solid-phase EIA test systems in the USSR use viral antigens produced by various methods. For example, the Rekombinant-HIV test system used an antigen genetically engineered; the Peptoskrin II and SPID-diagnostika test systems use synthetic antigen determinants; and the test systems produced by Antigen and NPO Vektor use viral lysate.

The quality of the analysis depends on, primarily, the sensitivity and specificity of the test system.

At present, most of the test systems used in the USSR have a lower level of sensitivity of 95 percent, which is why there are false-negative results. Data of the SNILEP [not further expanded] AIDS laboratory of the Central Scientific Research Laboratory of the USSR Ministry of Health confirm that. For example, of 75 sera obtained from Elista from HIV-infected children identified with the Organon Technika test system and confirmed with immunoblotting, seven sera yielded a negative result in the viral-lysate test system produced by the Antigen enterprise. In another instance, in testing of 20 sera that

contained antibodies to HIV, the SPID-diagnostika test system did not find the antibodies in two sera, and the Rekombinant-HIV system did not find them in one of the sera. Sera containing antibodies in a low titer fall into the false-negative category. Many such sera consist of sera from individuals who are in stage I of AIDS or children under two years of age.

In addition to inadequate sensitivity, the test systems named yield a low percentage of confirmation of positive results in confirmatory testing. Of 4,539 sera sent to the SNILEP laboratory as positive, the presence of HIV antibodies was confirmed in only 136 (2.96 percent).

Moreover, the percentage of positive reactions in solid-phase EIA in stage I of the screening varies from region to region, despite the fact that the same test systems are used in all the regions (Table 1). That can hardly be explained as just transportation conditions: the data for Belarus and Ukraine differ from each other by a factor of three. More than likely, the reason is in varying quality of analysis in the diagnostic laboratories.

**Table 1. Results of Solid-Phase EIA Testing of USSR Population for HIV Antibodies in 1989**

| Region    | Total tested | Positive EIA results |       |
|-----------|--------------|----------------------|-------|
|           |              | abs.                 | %     |
| USSR      | 29,146,056   | 17,391               | 0.060 |
| RSFSR     | 16,469,500   | 13,962               | 0.085 |
| Moscow    | 1,204,125    | 1,910                | 0.159 |
| Leningrad | 894,288      | 234                  | 0.026 |
| USSR      | 4,587,390    | 1,098                | 0.024 |
| BSSR      | 1,742,434    | 1,260                | 0.072 |
| UzSSR     | 1,556,105    | 183                  | 0.012 |
| KaSSR     | 1,351,946    | 161                  | 0.012 |
| GSSR      | 229,230      | 8                    | 0.003 |
| AzSSR     | 368,261      | 25                   | 0.007 |
| KiSSR     | 383,610      | 12                   | 0.003 |
| TaSSR     | 310,293      | 34                   | 0.011 |
| TuSSR     | 376,801      | 7                    | 0.002 |
| LiSSR     | 364,572      | 137                  | 0.038 |
| MSSR      | 577,424      | 424                  | 0.073 |
| LaSSR     | 382,089      | 77                   | 0.020 |
| ArSSR     | 149,713      | 0                    | 0.000 |
| ESSR      | 226,688      | 3                    | 0.001 |

The second stage of the diagnosis consists in confirmation of the results obtained in the screening of the sera. In the USSR, as in the rest of the world, immunoblotting is used as the confirmatory technique. Other techniques—radioimmune precipitation assay and immunofluorescence—are not widely used in the USSR because of the absence of commercial systems.



Immunoblotting does not require any special equipment, but the high cost of the test limits its use. In addition, interpretation of the immunoblotting results requires preliminary training of the specialist.

Based on the literature data,<sup>1-3</sup> as well as on WHO recommendations, an immunoblotting result is considered positive if the serum contains antibodies to at least one of the surface glycoproteins of the virus shell (molecular weight of the surface glycoproteins is 160, 120, and 41 kilodaltons). According to data produced at SNILEP, when DuPont blots are used, a result is considered positive if the serum contains antibodies to the glycoprotein with a molecular weight of 160 kilodaltons.

If there are antibodies to core proteins or viral enzymes, but there are no antibodies to shell glycoproteins, the result is considered indeterminate (Table 2).

**Table 2. Test Results Produced Done With DuPont HIV-1 Immune Blot**

| Molecular weight of HIV-I viral proteins, kD | Presence of antibodies to individual viral proteins, % |                    |                                   |
|--|--|--------------------|-----------------------------------|
|  | Sera containing HIV-I antibodies                       | Indeterminate sera | Sera containing HIV-II antibodies |
| 160  | 100  | -                  | -                                 |
| 120  | 86   | -                  | -                                 |
| 66   | 92.4   | 9.5                | 50                                |
| 55   | 85   | 26                 | 75                                |
| 51   | 85.8   | 28                 | 50                                |
| 45   | -  | 33                 | 100                               |
| 41   | 90.5   | -                  | -                                 |
| 40   | -  | 30                 | 100                               |
| 31   | 86   | 18                 | 100                               |
| 24   | 92.8   | 39                 | 100                               |
| 17   | 77.5   | 65                 | -                                 |

Table 3 presents data from our laboratory on the frequency of identification of antibodies to various viral proteins in indeterminate sera, as well as the most often encountered combinations of such proteins. When an indeterminate result is obtained, the individual to whom the serum belongs is removed from the donor list. Repeat testing of a new portion of the serum is done after three months. If an indeterminate result is obtained, analyses are done every three months for a year. Then if indeterminate results are still obtained or if the positive reactions disappear, observation of that individual is stopped, since an indeterminate result is not sufficient grounds for making a positive diagnosis. The reason for a false positive is the presence in the serum of antibodies that produce a cross reaction with the HIV antigens. More often than not, those antibodies are formed in autoimmune disorders, liver illnesses, tumor processes, etc.

**Table 3. Results of Testing of Indeterminate Sera With DuPont HIV-I Western Blot (IgG)**

| Number of bands in immune blot | Molecular weight of HIV-I proteins for which there are antibodies, kD | Number of cases |      |
|--------------------------------|---|-----------------|------|
|                                |   | abs.            | %    |
| 1                              | 17  | 64              | 37.9 |
|                                | 24  | 43              | 25.4 |
| 2                              | 17, 55  | 10              | 5.9  |
|                                | 17, 51  | 7               | 4.1  |
|                                | 17, 24  | 4               | 2.4  |
|                                | 24, 51  | 4               | 2.4  |
| 3                              | 17, 45, 55  | 8               | 4.7  |
|                                | 24, 45, 55  | 6               | 3.6  |
|                                | 24, 45, 51  | 5               | 3.0  |
| 4-5                            | 17, 31, 40, 45, 51  | 13              | 7.7  |
|                                | 17, 31, 40, 45, 55  | 5               | 3.0  |
|                                | 17, 31, 45, 51, 55  | 4               | 2.4  |

Moreover, as can be seen in Table 2, the results produced in the testing of sera containing antibodies to HIV-II with a DuPont blot designed to identify antibodies to HIV-I yield a picture similar to that of false-positive sera. For that reason, when an indeterminate result is obtained, it is necessary to perform additional testing for the presence of HIV-II antibodies.

The use of test systems that have high sensitivity and specificity makes it possible to improve the quality of the testing, and their use is economically justified. The data in Table 4 indicate the advantages of test systems such as Serodia-HIV, Organon Teknika, Wellcozyme, and Behringwerke. For that reason, it would be more useful, in our view, to perform an intermediate stage in which sera identified in the first stage of screening would be tested in test systems that have high sensitivity and specificity. For example, if the 4,593 sera that came to the laboratory have been tested right away with an immune blot, the total spent on the immunoblotting would have been \$152,947 (U.S. dollars), because the cost of one analysis with the immune blot is \$33.30 (DuPont, United States, 1989). The introduction of additional testing with the Serodia-HIV test system would reduce the number of sera needing testing in immune blot to 136, i.e., the cost of the tests done with the immune blot would fall to \$4,528.80. Based on the cost of the used Serodia-HIV test system, the total costs would be \$13,714.80, which is 11.2 times lower than the initial sum. The use of the Behringwerke test system would lower the cost 24-fold.

Based on the experience of testing sera from different contingents and checking the results obtained in other laboratories of the country, we propose the following algorithm for the confirming diagnostics.

**Table 4. Characteristics of Test Systems Used for Determining Antibodies to HIV-I**

| Test system     | Number of positive reactions (in %) in sera tested |                                    |               |
|-----------------|--|------------------------------------|---------------|
|                 | Containing antibodies to HIV-I                     | Not containing antibodies to HIV-I | Indeterminate |
| Organon         | 99.6   | 0.3                                | 5.9           |
| Behringwerke    | 98.2   | 5.3                                | -             |
| Genetic Systems | 99.0   | 5.6                                | 83.6          |
| Wellcozyme      | 98.3   | 0.3                                | 4.4           |
| Virgo           | 100.0  | 16.0                               | 63.6          |
| Biochrom        | 96.3   | 5.0                                | 60.0          |
| Serodia-HIV     | 100.0  | -                                  | 2.2           |
| DuPont          | 100.0  | 21.2                               | 93.5          |

Stage I, solid-phase EIA. When a positive result is obtained, the serum is tested again. If the positive result is confirmed, testing is done in the next stage.

Stage II, solid-phase EIA with test systems with high sensitivity and specificity. If a negative result is obtained, the analysis is performed again to rule out human error. If a positive result is obtained, testing is done in the next stage.

Stage III, immunoblotting. If an indeterminate result is received, testing is done in the next stage.

Stage IV, testing for HIV-II antibodies. If no HIV-II antibodies are found, serum from the individual is tested again three months later. If an indeterminate result is obtained again, the individual is tested every three months for a year.

The test result is transferred to the treating physician, who makes a diagnosis on the basis of the clinical and epidemiological data.

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#### <sup>3</sup>H-Tert-Butylbicycloorthobenzoate, Novel Ligand for Chlorine Ion Channel of GABA<sub>A</sub>-Receptor

927C0518G Moscow BYULLETEN  
EKSPERIMENTALNOY BIOLOGII I MEDITSINY  
in Russian Vol 113 No 2, Feb 92 pp 155-156

[Article by A. I. Golovko, G. A. Sofronov, Military Medicine Academy imeni S. M. Kirov, Leningrad; UDC 612.822:547.466.3].014.46.085.2]

[Abstract] The effect of <sup>3</sup>H-tert-butylbicycloorthobenzoate on the specific binding of <sup>35</sup>S-tert-butylbicyclophosphorothionate (<sup>35</sup>S-TBPT) to cerebral membranes was investigated using a synaptosomal mitochondrial fraction from mongrel albino male rats (180-200 g). It was shown that glass fiber filters GF/B and GF/C bound <sup>3</sup>H-TBOB better than <sup>35</sup>S-TBPT. In addition, nanomolar concentrations of GABA elicited an increase in the binding of the chlorine ion channel ligand. In conclusion, the GABA-recognizing portion of the receptor-ionophore complex allosterically affects the binding of <sup>3</sup>H-TBOB, as evidenced by the fact that GABA has a biphasic effect on the binding of the ligand with rat cerebral synaptic membranes and bicuculline completely negates the effects of the amino acid. Figures 2; tables 1.

#### Levamin and Cerebrollysine as Immunostimulants

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[Article by G. A. Belokrylov, I. V. Molchanova, Experimental Medicine Institute, USSR Academy of Medical Sciences, Leningrad; UDC 615.272:547.466].017:615.275.4].076.9]

[Abstract] The immunostimulant effects of levamin and cerebrollysine, mixtures of immunoactive and inactive amino acids, were compared with thymopentin on 270 male CBA mice (14-16 g). The substances were administered subcutaneously or orally daily for five days in various doses. The animals were then immunized intravenously with ram erythrocytes or Vi-antigen and four days later the number of IgM antibody-producing cells was counted. Levamin (1 - 1 x 10<sup>-6</sup> µg) and cerebrollysine (1 - 1 x 10<sup>-4</sup> µg) increased IgM antibody-producing cell production by 2 - 2.2 times and 1.6 - 3.1 times, respectively. Thymopentin was active only in a range of 1 - 1 x 10<sup>-2</sup> µg, and increased antibody-producing cell production by 2.4 - 2.5 times. The preparations had no effect on the immune response to the thymus-independent Vi-antigen. The data show that the mixtures of amino acids can induce the Thy-1-antigen to T-precursors, like thymic peptides, and thus amplify the thymus-dependent response without affecting the level of the thymus-independent response. However, the amino acid mixtures can increase the immune response both orally and parenterally, in contrast to the thymic peptides. In conclusion, amplification by the mixtures and thymopentin of the thymus-dependent immune response alone shows that their effects are associated with the function of T-cells, but not B-cells. Tables 2; references 7: 4 Russian, 3 Western.

**Neurotransmitter Support of Immune System  
Organs Under Conditions of Benzpyrene  
Intoxication**

927C05181 Moscow BYULLETEN

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[Article by Yu. I. Borodin, V. A. Izranov, N. A. Sklyanova, A. V. Semenyuk, Clinical and Experimental Lymphology Scientific Research Laboratory, Siberian Department, USSR Academy of Medical Sciences, Novosibirsk; UDC 612.017.1-02:615.917:664.44]

[Abstract] The transmitting background of the adrenergic nervous component of immune organs was investigated in female rats given 20 mg/kg benzpyrene intraperitoneally on days 10-12 of pregnancy for a total dose of 60 mg/kg. The progeny of both the control and

experimental cohorts were then given 30 mg/kg benzpyrene for two days and monitored for two-four months. It was shown that acute administration of benzpyrene to control progeny depletes transmitters in the lymphoid tissue. In contrast, prenatal administration of the substance suppresses adrenergic structures of the lymphoid organs. The decrease in the neurotransmitter status of pubertal progeny exposed in utero indicates the "imprinting" of the reaction to benzpyrene by elements of the adrenergic system. Those animals surviving in utero exposure apparently acquire post-natal resistance of the immune system organs to benzpyrene and have a lower level of neurotransmitter support of the lymphoid organs. In conclusion, it is possible that administering benzpyrene to pregnant animals has a "conditioning" effect on the immune system organs of the progeny when the body encounters the substance for a second time. Tables 1; references 6: Russian.

**Rat Heart Adenylate Cyclase Regulatory Properties During Toxic Shock Caused by Plague**

927C0518J Moscow BYULLETEN

EKSPERIMENTALNOY BIOLOGII I MEDITSINY

*in Russian Vol 113 No 2, Feb 92 (manuscript received 19 Jun 91) pp 172-174*

[Article by T. D. Cherkasova, V. A. Yurkiv, V. P. Avrorov, and A. V. Griboyedov, Epidemiology Central Scientific Research Institute, USSR Ministry of Health, Moscow; UDC 616.12-008.931-92:615.919:579.848.95]092.9]

[Abstract] The effect of "murine" plague toxin (1 mg, LD<sub>100</sub>, intraperitoneal injection) on adenylate cyclase activity in the rat heart was investigated. The results suggested that the "murine" toxin does not affect the

GTPase activity of N-proteins in the adenylate cyclase complex or coupling with catalytic components *in vivo*, in contrast to the effect exerted by many bacterial toxins. In addition, it was shown that the catalytic subunit of adenylate cyclase in the heart is activated most by plague intoxication. Two hours after the toxin was administered, the sensitivity of adenylate cyclase in the heart to the regulating effect of catecholamines, glucagon, and histamine had not changed. This suggests that the molecular pathway of the damaging effect of "murine" plague toxin is not due to the inactivation of adenylate cyclase bound with these hormonal receptors. It is possible that during plague toxic shock the coupling of hormonal receptors with adenylate cyclase is disturbed due to changes in the lipid composition of the cardiac plasma membrane in the experimental rats. Figures 1; tables 1; references 15: 5 Russian, 10 Western.

### Molecular Mimicry as a Factor in the Pathogenicity of Microorganisms

927C0514A Moscow USPEKHI SOVREMENNOY BIOLOGII in Russian Vol 111 No 2, Mar-Apr 92 pp 225-237

[Article by L. M. Pinchuk, Non-Black Earth Zone Veterinary Scientific Research Institute of the Russian Federation, Nizhniy Novgorod; UDC 616-097:612.017.33:577.12]

[Text] The phenomenon of molecular (epitopic) mimicry, which makes it possible for microorganisms to resist antibody-dependant reactions of the host through crossed immunoreactivity, is reviewed. Epitopic mimicry, which is associated with the structural homology of proteins of evolutionarily remote organisms, with the antigenic variability of bacteria, and with the quasi-species nature (extreme genetic heterogeneity) of certain viruses, distorts the immune response, and not only blocks the formation of antibodies to foreign agents, but also disrupts tolerance of mammals to their own antigens, thus provoking severe autoimmune diseases. The point of view is advanced that epitopic mimicry comprises a part of a more total, general biological phenomenon of molecular mimicry, by means of which the regulation of physiological and immune reaction (ligand-receptor and idiotypic-anti-idiotypic interactions) are accomplished.

Pathogenicity is usually defined as the capacity of a parasite to cause a disease. Pathogenicity may be considered not only from the functional perspective, but also as a particular instance of an interaction of living organisms belonging to different kingdoms of nature, of which biomolecules serve as the material carrier.<sup>58</sup> Within the framework of the general biological concept, interactions between living organisms arise at the earliest stages of evolution in the form of the recognition of "self" and "nonself", and are effectuated through the system of protein cooperation.<sup>14</sup> According to the biomolecular model, pathogenicity can be defined as the property of microorganisms to elaborate specific functionally active substances (factors of pathogenicity), the materialization of which in the host organism leads to

the development of an infectious process. We are discussing one of the molecular genetic aspects of the problem of the overcoming by microorganisms of the defensive barriers of the host.

The term "molecular mimicry" appeared at the beginning of the 1980's, when it became clear that monoclonal antibodies to a number of viruses were capable of reacting with the antigens of mammals and man. Out of 700 monoclonal antibodies to a 14 different viruses, 4 percent specifically bind with proteins expressed by human cells.<sup>73, 74</sup> It should, however, be noted that the name of the phenomenon is evidently does not entirely appropriately reflect the essence of the problem which are considered under this rubric in the scientific literature, and it would be more precise in this case to use the term "epitopic mimicry". The phenomenon of molecular mimicry is probably broader, and has a general biological sense (see below).

Several mechanisms of molecular mimicry can be delineated which make it possible for pathogenic microorganisms to resist antibody-dependant reactions of the host through crossed immunoreactivity: 1) the homology of amino acid sequences of related proteins in organisms, which are different stages of evolution (for example, the similarity of the primary structures of the dehydrogenases and aminotransferases of bacteria and vertebrates is 30-40 percent<sup>70, 98</sup>); 2) stochastic (probabilistic) analogies of individual regions of proteins in organisms which are evolutionarily far removed from one another (including as the result of convergent evolution)<sup>25</sup>; 3) the antigenic variability of microorganisms which is associated with the plasticity of their genetic material and the occurrence of random imitations of determinants of host proteins, which makes it possible for them to evade the influence of the immune system (in imitation of "self"), or to elicit the formation of autoantibodies against the host's own tissues when normal presentation is disturbed<sup>73</sup>; 4) the imitation of certain physiologically active metabolites and structures (for example, hormones, pilins, etc.) and the use of the receptors of these proteins to facilitate the adhesion and invasion of bacteria, and the overcoming by them of the the host's natural tissue barriers.<sup>50</sup>

Some examples of molecular mimicry of the proteins of microorganisms and mammals are given in Tables 1 and 2, with indication of the physiological consequences for animals and man.



Table 1. Immunological and Structural Homology of Proteins of Bacteria and Vertebrates

| Proteins of bacteria   | Proteins of vertebrates   | Physiological consequences of the phenomenon  | Reference    |
|--|---|---|--------------|
| Peptide of <i>Escherichia coli</i> protein, containing the sequence Asn-Leu-Ala-Ala-Ser-Ser-Thr                                | Soluble retinal protein (S antigen) or M-peptide of S antigen   | Symptoms of experimental autoimmune uveitis with the formation of autoantibodies against the animals' normal proteins   | [88]         |
| <i>Klebsiella pneumoniae</i> nitroreductase  | HLA-B27 transmembrane protein of man  | Development of reactive arthritis in people with HLA-B27 <sup>+</sup> phenotype. Lysis of B27 <sup>+</sup> lymphocytes by rabbit antiserum against <i>klebsiellae</i> in patients with ankylosing spondylitis. The presence of receptors for <i>klebsiellae</i> on these lymphocytes  | [3, 44, 99]  |
| Ye2 protein of <i>Yersinia pseudotuberculosis</i> Nos. 73 and 78; 19 kilodalton protein of <i>E. coli</i> No. 3374             | HLA-B27 protein of man (region 69-89, responsible for allotypic specificity)                              | HLA-B27 antibodies react with cells of ankylosing spondylitis patients  | [30, 99]     |
| Vi-antigen of gram negative bacteria; type-specific polysaccharide of type XIV pneumococci; receptors for <i>E. coli</i> pili  | Human blood group antigens  | In individuals with secretory status (i.e., producing MHC antigens in biological fluids), the adhesion of bacteria decreases. The antigens of bacteria are not recognized by the human immune system as foreign. The selection of human allotypes which are resistant to infections takes place in natural foci (for example, to cholera in the Ganges River delta, and so forth) | [23]         |
| <i>Staphylococcus aureus</i> protein   | Isoantigens of group A erythrocytes (group B to a lesser extent)  | Predisposition to septicemia and chronicity of staphylococcal infections in patients with group A blood is greater as compared with patients with group B blood   | [7]          |
| Antigens of enterobacteria and streptococci  | Proteins of human arteries  | Disease of vessels  | [84]         |
| M protein of types 5 and 6 streptococci  | Proteins of myocardium of mammals   | Lymphocytes activated by M proteins exert a cytotoxic effect on heart cells, inducing rheumatic disease of the organ  | [20, 60, 93] |
| 43 kilodalton epitope of M protein of group A streptococci, serotypes 6 and 12   | Proteins of human renal glomeruli   | Acute proliferative glomerulonephritis and other autoimmune diseases  | [51]         |
| Peptides 84-116 and 184-197 of M protein of type 5 group A streptococci  | Myosin of rabbit muscles and human cardiac muscle   | Autoimmune heart disease  | [35, 36, 46] |
| Polysaccharides of group A streptococci  | Epidermal antigens of epithelial cells of thymus and basal layer of skin                                  | Formation of autoantibodies which is accompanied by acute primary rheumatism and lesion of the thymus. The appearance of cytotoxic lymphocytes which lyse cells of lymph nodes and spleen   | [1, 10]      |
| <i>Mycoplasma pneumoniae</i> antigens  | Ii antigens of membranes of human erythrocytes  | Formation of cold agglutinins which induce autoimmune hemolysis and acute hemolytic anemia in pneumonia patients. The appearance of autoantibodies to tissues of brain, lungs, liver, heart, smooth muscles, lymphocytes, etc.  | [43]         |
| 64 kilodalton protein of <i>Yersinia enterocolitica</i> and proteins of 8 species of other bacteria                            | Human thyrotropin   | Hyperthyroidism (Graves' disease). Synthesis of autoantibodies competing for thyrotropin receptors of the thyroid gland and reproducing the biological effects of thyrotropin   | [28, 54]     |
| Fc-binding region of the Cowan strain of <i>S. aureus</i> protein A and analogous proteins of streptococci                     | IgM and IgG rheumatoid factors isolated from from patients with rheumatoid arthritis and cryoglobulinemia | In the immune response to the infectious agent rheumatoid factors (antibodies to self immunoglobulins) are induced or modulated through the anti-idiotypic mechanism of internal reflection. The attenuation of immunity through the elimination of IgM and IgG antibodies  | [75]         |
| 65 kilodalton protein of <i>Mycobacterium tuberculosis</i> and other mycobacteria. <i>E. coli</i> protein coded by gene Gro EL | Stress proteins of eukaryotic cells   | Epitopes of conservative regions of proteins of mycobacteria are not recognized by T cells as foreign, thus causing either autoimmune pathology or tolerance to infectious agents   | [32, 97]     |

Note: MHC - major histocompatibility complex; IgG and IgM - immunoglobulins G and M, respectively.

Table 2. Immunological and Structural Homology of Proteins of Viruses and Vertebrates

| Proteins of viruses  | Proteins of vertebrates  | Physiological consequences of the phenomenon   | Reference    |
|--|--|--|--------------|
| EBNA-1 nuclear protein of Epstein-Barr virus   | Human collagen I and III and keratin I and II  | Decrease in the immune response to the Epstein-Barr virus. The capacity of T lymphocytes to suppress the EBNA-1-induced proliferation of B lymphocytes is disturbed in rheumatoid arthritis patients; this leads to the hyperproduction of antibodies cross-reacting with collagen and keratin   | [90]         |
| gp 110 glycoprotein of Epstein-Barr virus (sequence Gln-Lys-Arg-Ala-Ala-Gln-Arg-Ala-Ala) | The sequence Gln-Lys-Arg-Ala-Ala localized in the third region of the DR $\beta$ -chain molecule of HLA-Dw4        | Susceptibility to rheumatoid arthritis associated with a T cell epitope on the DR molecule of the $\beta$ -chain of HLA-Dw4. The Epstein-Barr virus, which has an homologous determinant, may cause disease in humans  | [81]         |
| Epstein-Barr virus   | C3 and C3dg components of complement, which interact with the CR2 receptor   | The interaction of C3 and C3dg components of complement, which interact with the CR2 receptor, induce the proliferation of human B cell lines. Since CR2 is also a receptor for Epstein-Barr virus, this explains the T-independent B-mitogenic properties of this virus   | [53]         |
| Measles virus  | Surface antigens of human T suppressors and T helpers  | Development of immunomodulating effects in measles infection   | [21]         |
| Glycoprotein of the rabies virus   | Fox brain glycolipid   | The structural homology of proteins facilitates the penetration of the virus into the brain under the guise of "self" and prevents the formation of antiviral antibodies.  | [55]         |
| Protein from the IE-2 immediate-early region (region 82-96) of cytomegalovirus           | The $\beta$ 1-chain of HLA-DR glycoprotein molecule (region 53-57) on the surface of human B cells and macrophages | Graft rejection reaction develops in viral infection   | [47]         |
| Secretory polypeptide of smallpox vaccination virus                                      | Control proteins of complement (CPC)   | CPC blocks complement-mediated induction of the inflammatory process and lysis of bacteria and viruses. Virus factors homologous to CPC regulate cell metabolism for the support of their own replication in the cell  | [61]         |
| gp 46 glycoprotein of HTLV-1 virus membrane  | The hIL2 region, which participates in the binding of the $\beta$ -receptor  | HTLV-1 virus-transformed T cells express 5-10 times more IL-2 receptors than normal T cells. The capacity of HTLV-1 [as published] to react through gp 46 with IL-2 receptors on T cells on the one hand facilitates the penetration of the virus into these cells, and on the other hand disrupts the chain of intercellular interactions associated with the proliferation of T cells  | [57, 59]     |
| gp 41 protein of HIV (region 837-844)  | The $\beta$ -chain of class MHC molecules (region 19-25)   | Formation of immunosuppressant autoantibodies and decrease in immunity against the virus   | [49, 63]     |
| The octapeptide T of the main membrane glycoprotein of HIV-1                             | Thymosin $\alpha$ 1  | Thymosin $\alpha$ 1 stimulates a number of important functions in the cellular immunity system, and its deficiency leads to the appearance of symptoms reminiscent of AIDS. HIV competes for thymosin $\alpha$ 1 receptors and, by binding with them, induces a disturbance in the functional regulation of T lymphocytes. An antiserum against thymosin $\alpha$ 1 should intensify defensive reactions of the organism against the virus | [72, 83]     |
| Region 92-109 of HIV p17 protein   | Thymosin $\alpha$ 1 (region 11-28)   | —  | —            |
| 120 kilodalton external glycoprotein of HIV  | Region of CD4 HLA molecule of T helpers  | The CD4 molecule serves as a receptor for HIV. The protective response to HIV infection is lacking due to inborn tolerance to immunodominant gp 120 sites. Development of immunosuppression  | [18, 62, 69] |
| Transmembrane region of gp 41 protein of HIV   | Region of IL-2 (Leu—Gly—Gln—Leu—Leu—Leu)   | Autoantibodies against IL-2 are found in sera of AIDS patients. The IL-2 level in the organism is depressed, but the number of IL-2 receptors is increased. gp 41 hexamer is responsible for the immunosuppressant and cytolytic action of HIV   | [27, 64, 79] |
| Protein—a product of gene env (region 850-855) of HIV                                    | Region 34-39 of IL-2 (Leu—Gly—His—Leu—Leu—Leu)   | —  | —            |

Note: HIV - human immunodeficiency virus; IL-2 - interleukin 2.

The molecular-genetic mechanisms of the antigenic variability of bacteria have been reviewed in detail in the review article of Tets and Borisova [19]. The most intense antigenic variability is observed in intragenomic reorganizations; it is regulated at the lowest rate by extrachromosomal factors and by means of induced mutagenesis; the influence of spontaneous mutagenesis is least significant. The mutational nature of the S-R dissociation of brucellae, enterobacteria, and mycobacteria, of the formation of L-forms, and the occurrence of different serovars of pathogenic escherichiae has been proven [4, 5, 15]. Variations in antigenic structure have been noted during the treatment of patients with various medicinal preparations, for example, derivatives of the nitrofur series; metabolites of tissues of the organism such as peroxides, nitrosamines, DNA molecules and other compounds also exert a mutational effect [8]. The abrupt appearance of mutants of *Escherichia coli* O124 during infection in the guinea pig correlates with an increase in specific defense factors of the animals. Instances of change in the antigenic structure of the cilia of gonococci during the illness, change in the serovars of vibrios in volunteers, phasic variations of salmonellae, and transformations of capsular polysaccharides and lipopolysaccharides of escherichiae are widely known. Antigenic variability in *E. coli*, *Shigella sonnei*, *Mycobacterium* sp., *Bacillus brevis*, *Pseudomonas aeruginosa*, and other species is associated with extrachromosomal factors of heredity (phages, plasmids, transposons, IS elements) [17].

Modifications of the composition of cellular proteins allow microbes to elude defense mechanism of the immune system of vertebrates, and antigenic mimicry is one of the factors of the pathogenicity of microorganisms. For example, mycoplasmas may persist in the body of the host for a long time, since they possess antigens in common with tissues of man, cattle, and chickens, and it is thus far difficult to state whether the presence of cross-reacting antigens is caused by change in the genome or by uptake of host antigens and their incorporation into the cells of mycoplasmas [16, 33]. In addition, diseases induced by mycoplasmas are, as a rule, complicated by the development of autoimmune and other pathological states associated with the paradoxical feature of the recognition of antigens by T cells which are reacting to a greater degree to their own altered antigens than to foreign antigens which are like their own. This may indirectly suggest that the basic (more ancient) function of the immune system, is an oversight function, consisting in the recognition and elimination of self cells with an aberrant phenotype.

Given the presence of identical regions in proteins of organisms which are at different stages of evolution, the immune system of vertebrates would operate with greater "noise" (errors) if products of the major histocompatibility complex (MHC), found on the surface of all cells, did not participate in the presentation of antigens. It has been possible in recent years to decipher certain stages of the very complex phenomenon of

immunological recognition. Only 10-20 percent of the absorbed protein remains in macrophages in the form of fragments during the processing of antigens; at the same time, the antigenic determinants of the native molecule disappears as a rule, and re-expression and localization on the membrane of the macrophage of these fragments are determined by their capacity for trimolecular interaction with the receptor of T cells and the Ia molecule [6]. The molecular structure and principles of the organization of the processing regions are diverse; they are distinguished topographically from the antigenic determinants and most often the form of an  $\alpha$ -helix. The amino acid sequence of peptides (Val-His-Ala-His-Ala) for their binding with the Ia<sup>d</sup> MHC molecule of mice is known. Denatured antigens react more readily with the Ia molecule; some T cells recognize such antigens without processing [87]. The viruses of influenza and vesicular stomatitis and a number of other viruses associate weakly with the MHC molecule, and possibly for this reason the specific response to these viruses is attenuated.

The T-receptor is capable of clearly differentiating fine conformational changes which arise in the variation of epitopes of an antigen which are associated with the MHC molecule, perceiving the complex as a whole, and the smallest differences in the structure of the associate or its coincidence with another lead to a sharp decline in the activity of the T-receptor for this epitope or to the appearance of a crossed reaction of the same receptor to the foreign epitope. Each of the three molecules has at least two regions (two valencies) for contact with each of the two other molecules, and the substitution of even one amino acid in any of these elements may cancel the reaction of the T cells to the antigen. So complex a principle of recognition, in combination with the extreme lability of the class II MHC molecules, the influence of the affinity of the T-receptor, and the inclusion of diverse combinations of substances of intercellular interaction and other factors as well, leads to the fact that the T cells react to a single epitope or to a small number of them (sometime one to two amino acids are decisive for recognition), while the synthesized antibodies are specific for the whole protein molecule. Autoimmune effects arise upon the activation of T cells by self antigens, in the structure of which fragments interacting with MHC products are contained.

Tolerance to self proteins is supported in the norm by means of various structures, including anti-idiotypic antibodies and suppressor T cells. Autoimmunity is formed in the presence of an unusual presentation of antigens which is provoked both by external factors (cross-reacting proteins of microorganisms) and by internal processes (aging and malignant transformation of cells, breakdown of regulatory mechanisms, defective microdefibrination, in which intracellular components which have entered the extracellular space during the destruction of cells, are removed insufficiently rapidly) [76]. Computer analysis of 2511 amino acid sequences of proteins of viruses and man has identified 2469 identical

hexamers, 186 septomers, and 17 octamers [74]. Bearing in mind that the average size of peptides recognized by T cells is 7-13 amino acids, similar regions may in a number of instances determine the processing of viral proteins in the host organism and induce autoimmune diseases.

The Epstein-Barr, herpes simplex, and influenza viruses, adenoviruses, and a number of others which have antigens in common with host tissues elicit: a) polyclonal activation of B lymphocytes and their differentiation into plasma cells which synthesize antibodies; b) polyclonal stimulation of "dormant" B lymphocytes which carry receptors for self antigens; c) reactions at the level of idiotype-anti-idiotype interactions which activate autoimmune B lymphocytes [48]. Following the *in vitro* infection of human peripheral blood B lymphocytes with the Epstein-Barr virus, it was established that 33 percent of the immunoglobulin-secreting cells produce autoantibodies and that the majority of the lines do so to more than five antigens [85]. Antiviral antibodies in AIDS patients manifest the activity of autoantibodies to the CH1 domain of human immunoglobulin in connection with the homology of the one of the regions of the membrane glycoprotein gp 120 of the human immunodeficiency virus and the heavy chain of immunoglobulin [89]. It has been demonstrated experimentally that the expression of class I and II MHC antigens in T lymphocytes changes during infection with the virus of influenza A/HK, which is expressed in increased binding of specific antibodies by these human antigens and correspondingly in the disturbance of the process of presentation in T cells. (Evidently the effect is associated with the effect of viral neuraminidase which catalyzes the removal of sialic acids from the surface of the cells) [80].

The molecular mechanisms that govern the disruption of the tolerance of organisms to their own antigens have been insufficiently studied. It is known that epitopic mimicry depends to a greater degree on the configuration of the chains of the site, which is perceived in reverse (mirror) orientation, than on the carbohydrate stabilizing frame of the molecule [71]. The 57th position of the DQ  $\beta$ -chain of the MHC and the Vp genes are of significance in the predisposition to autoimmune diseases. Macrophages, by interacting with the phospholipids of membranes (one of the earliest and most primitive recognition signals), as well as with carbohydrates and peptides, recognize altered "self" [6]. More than 100 specific autoantibodies have been recognized that react with human antigens (surface and intracellular proteins, substances of the intercellular space and biological fluids), some of which are encountered in healthy individuals, and some in people with severe autoimmune diseases provoked by viruses and bacteria [45, 46]. For example, the autoantibodies to cytoplasmic myeloperoxidase of neutrophils have been identified in patients with viral infections, glomerulonephritis, and systemic vasculitis; they possess the capacity to penetrate into the cytoplasm of living granulocytes without binding with the Fc receptor, and induce degenerative changes and lysis in target cells [95].

Let us consider as an example the forms of the organization of the immune response which arise in response to the so-called heat shock proteins (HSP) which participate in important metabolic processes, the translocation and secretion of proteins, proteolysis, the binding of ATP, the suppression of DNA replication, etc [78]. The HSP are a family of evolutionarily conservative proteins which are expressed in all organisms, from the prokaryotes to man, in unfavorable conditions, including thermal and oxidative injuries. For example, with a shift in temperature from 37 to 43 degrees, 19 and 37 proteins, respectively, have been identified by the gel electrophoresis method in *Neisseria gonorrhoeae* with types I and IV colonies [56]. The HSP are characterized by a high degree of homology: more than 50 percent of the amino acid residues in bacteria and mammals are identical; the HSP of 65 percent of mycobacteria and *E. coli* are similar with respect to primary structure, and in *Mycobacterium tuberculosis* and *Mycobacterium leprae*, this is true in 95 percent [66, 97].

The presence of variable and constant regions in HSP, some of which are T cell epitopes (their position is well known), makes it possible to use these proteins to decipher the pathways of the formation of different types of immunity: determinants from variable regions are recognized by T cells of the human immune system as foreign, and induce a protective response, while the conservative regions, which are similar to the self proteins of the macroorganism, stimulate the development of the autoimmune process. It is known that the T cell epitopes and determinants that react with antibodies do not coincide in the molecule of a 65 kilodalton protein of the mycobacteria which is coded by the gene Gro EL. It was shown through a study of five antigen epitopes that human T cell lines and clones recognize two of them as self (regions 195-219 and 390-412). It is assumed that both aggressive autoimmune injuries of the nervous system, which are observed in tuberculoid leprosy and the tolerance to foreign antigens in lepromatous leprosy, when the organism does not react to an extraordinary concentration of mycobacteria,  $10^9$  cells per g of human tissue, are associated with the presentation of conservative epitopes by antigen-presenting cells [97].

The potential role of HSP in the induction of the autoimmune response has been proven experimentally: T cells that react to mycobacterial antigens are capable of provoking an autoimmune disease in rats, so-called adjuvant-induced arthritis that develops in the animals after their injection with complete Freund's adjuvant. If the rats are immunized with HSP of mycobacteria before the introduction of the adjuvant or autoreactive T cells are imported into them, the disease does not develop [32, 96]. An analogy has been noted between the reaction of the organism to a temperature effect and the etiology of rheumatoid arthritis and other diseases of the joints [24].

In addition to the exchange of substances and energy with the external milieu, the exchange of information between cells and tissues is extremely important for the



macroorganism. The basic type of intercellular communication is interaction by means of biologically active substances, hormones, mediators, neuropeptides, etc. Signal recognition and processing systems are present in perceiving cells, the receptors, which recognize and transform this signal into a chain of intracellular events that conclude with a physiological response (so-called ligand-receptor interactions) [14]. There is another point of view that presumes the ligand acts only as a trigger and that all the information for the activation of the target cell is coded in the receptor molecule, which sets off the cascade of biochemical reactions.

Pathogenic bacteria overcome the tissue barriers of the host, thus coming into contact with the surface structures of cells, and molecular mimicry is one of the mechanisms of this process: legends [as published] of the bacteria have fragments of molecules analogous to the binding sites of some natural physiologically active substances of the host. For example, adhesins (pilins) of *E. coli* contain domains that react specifically with gangliosides initially designed for the reception of signals from peptide hormones [11]. Proteins have been found in *E. coli*, *N. gonorrhoeae*, *Yersinia enterocolitica*, *Shigella*, and *Staphylococcus aureus* which imitate insulin, gonadotropin, and calmodulin [50]. Antibodies against the receptors of these proteins have not infrequently been identified in man, and their occurrence is accompanied by the development of severe autoimmune injuries. Thus, antibodies against the insulin receptor that react with the  $\alpha$ -chain of the insulin receptor by means of two epitopes (regions 277-299 and 705-731), as well as antiviral antibodies with the properties of autoantibodies (due to common antigens) that intensely destroy the  $\beta$ -cells of the pancreatic islets, are present in diabetes [40, 52, 82]. In severe myasthenia, accompanied by an alteration in the migration of activated cells in the normal thymus, autoantibodies against the acetylcholine receptor, and bacterial, and viral infections serve as the provocative factor, including the herpes simplex virus which has antigens in common with human cells: mimicking epitopes on the D glycoprotein of the herpes simplex virus (region 286-293) and amino acid residues 160-167 of the acetylcholine receptor are distinguished only by one amino acid, which determines the cross-immunoreactivity [31, 39, 41]. New antiviral preparations are modeled both as imitation ligands or imitators of receptors which competitively replace natural components in the interaction of the virus with the host cell [65]. Such diseases of the thyroid gland as Basedow's disease, Hashimoto's thyroiditis, and Graves' disease are associated with the formation of autoantibodies against the receptor of thyroid-stimulating hormone, as well as of antibodies against thyroglobulin and the peroxidase of thyrocytes and other proteins which lead to various diseases of the thyroid gland [68, 77]. In Hashimoto's thyroiditis infiltration is observed of tissue of the gland by CD4<sup>+</sup> and CD8<sup>+</sup> T cells which produce interleukin 2 and  $\gamma$ -interferon, and the lymphocytes manifest antibody-dependant cytotoxicity [29, 91]. The authors of these studies [29, 91] conjecture that the disease is induced by

bacterial infections, since proteins of *E. coli* and *Y. enterocolitica* cross-react with thyrotropin.

More than a few data have by now been accumulated that suggest that epitopic mimicry may be regarded as a part of a more total, general biological phenomenon of molecular mimicry, by means of which, for example in mammals, the regulation of physiological, immune, and autoimmune reactions are accomplished in accordance with the feedback principle. Antibodies to small, biologically active ligands (neuropeptides, hormones) copy the characteristics of receptors, while antibodies to the antigens of hormone-producing cells imitate the effects of physiological regulators [13]. In their turn anti-idiotypic antibodies copy some properties of ligands. In addition to the receptors of various compounds, an idiosyncratic form of receptors and their anti-idiotypic equivalent are simultaneously present on the surface of cells of the macroorganism and on the membranes of the inner compartment [2].

The formation of anti-idiotypic antibodies is associated with the fact that variable regions of antibodies are unique and, consequently, immunogenic [22]. Thus, these molecules are directed against the same antibodies, and if antibodies are synthesized against the active center, they may carry an "inner image" of the antigen. This has been demonstrated experimentally based on the example of anti-idiotypic antibodies against the active centers of mouse antibodies to dinitrophenol, which imitate the antigen [52]. Anti-idiotypic antibodies are present as a spatial and sometimes functional likeness of antigens that induce the elaboration of the primary antibodies. They may imitate practically any molecule in the organism or in the external milieu surrounding it; at the same time proteins that differ markedly with respect to their amino acid composition, even with respect to 137 amino acid residues out of 141, not infrequently have an identical conformation [42]. Anti-idiotypic antibodies against the ligands of receptors may be regarded as a factor of the mimicry of these ligands or as a structural homolog of anti-idiotypic antibodies against cell receptors. In the first case they imitate the interaction of the antigen with the receptors of membranes, and in the second, antibodies against ligands on cell membranes [34]. This is the basis of their wide application for the study of the receptors of hormones and neuromediators, while the antireceptor anti-idiotypic antibodies are used as complementary reagents for the study of membrane receptors [67]. By mimicking biologically active substances, anti-idiotypic antibodies participate in the modulation of physiological activity of the organism in the norm and in pathology, provoking the development of a number of diseases [9]. It has been demonstrated [94] that anti-idiotypic antibodies against antibodies to the HA3 region of retroviruses imitate the immunological, functional, and molecular properties of this region of the viruses, which opens up possibilities for the creation of new anti-idiotypic vaccines, the action of which is not associated with the sensitization of the organism by foreign substances or the possibility of



infection by pathogenic agents upon reversion of their properties. Another promising direction in the creation of vaccines is the construction of synthetic peptides which imitate specific regions of an antigen, epitopes that are capable of being recognized by T cells, but which do not induce the phenomenon of autoimmunity.

Let us note in conclusion that the questions touched upon in this article are related in one degree or another to the general biological phenomenon of molecular recognition. In nature monotypal cells are associated by means of complementary fragments of the cell surface. The complementarity arises initially as the result of the natural process of cell division in which the daughter cell constitutes a likeness, the mirror reflection of the maternal cell [37]. The surface of each cell's complementary regions and in the higher animals the contact of cells is accomplished in combination with MHC proteins. The capacity for recognition of macromolecules is not limited only to the immune system, which enables macroorganisms to eliminate foreign agents with a high degree of efficiency and to preserve the integrity of the system and controllability. A more ancient level of regulation, characterized by uniformity, narrow specificity, and genetic stability (ligand-receptor interactions), is also preserved in mammals [9]. Higher organisms control the intensity of physiological and immune reactions by means of the imitation or copying of diverse compounds of the external and internal milieu, while molecular mimicry in the pathogenic bacteria serves as one of the principal tools for overcoming the defensive factors of the host. Despite the fact that study of the elements of molecular recognition is at the beginning stage, on the basis of this conception, a number of promising directions of an applied character have been developed that are important for the further development of biotechnology: the creation of vaccines of a new generation, the construction of antiviral agents on the basis of imitation ligands and imitators of receptors, the highly selective extraction of medicinal chemicals with the use of receptor groups on polymers, etc.

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### Pharmacological Characteristics of a New Anticholinesterase Drug, Aminostigmine

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[Article by V. B. Prozorovskiy, L. V. Pavlova, I. M. Suslova, N. I. Shchemeleva, Scientific Research Institute of Military Medicine, USSR Ministry of Defense, St. Petersburg; UDC 615.217.32.07]

[Abstract] The cholinesterase inhibitors patented in the United States on the basic carbamate esters of 2-substituted derivatives of 3-oxypyridine do not produce an adequate insecticidal effect. The Scientific Research Institute of Military Medicine of the USSR Ministry of Defense synthesized and studied one of the substances of that group—N,N<sup>1</sup>-dimethyl-(2-N<sup>1</sup>,N<sup>1</sup>-dimethylaminomethyl-pyridyl-3) carbamate dihydrochloride. The substance, otherwise known as aminostigmine, has been accepted for wide clinical use in the form of a 0.1 percent solution for treatment of cholinolytic poisoning. Aminostigmine has marked anticholinergic and anticholinesterase activity that is roughly similar to that of physostigmine. It has a primarily M-cholinopotentiation action on the body as a whole and on individual organs. In animal testing, tolerance to aminostigmine was found to be highly species-specific. The route of administration made little difference in the LD<sub>50</sub> studies, suggesting that bioaccessibility is high, with weak elimination by the liver. Figures 1, references 8: 3 Russian, 5 Western.

### Elevated Sensitivity of Rats to Ouabain in Acute Stage of Cardiac Insufficiency

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[Article by Ye. A. Gorodetskaya, E. A. Allabergenova, O. S. Medvedev, Laboratory of Experimental Pharmacology, All-Union Cardiac Science Center, USSR Academy of Medical Sciences, Moscow; UDC 615.222:547.918].03:616.12-008.46-036.11].06.076.9]

[Abstract] In the context of an effort to develop a model of cardiac insufficiency that adequately reflects the clinical signs of that pathology, the researchers here report work that represents a continuation of the development of a technique for creating the acute stage of the pathology in rats via embolization of coronary arteries with radioactive microspheres. The work focused on studying overall and regional hemodynamic characteristics of the model rats in a waking state 48 hours after embolization, as well as on the response of the cardiovascular system to the cardiac glycoside, ouabain. The microspheres were introduced into the left ventricle during occlusion of the ascending artery. The rats were found to exhibit elevated sensitivity to the ouabain that manifested itself as marked vasoconstriction in a number of organs—i.e., the skin, the stomach, the pancreas, the small

intestine, the diaphragm, and the kidneys—which led to a substantial elevation in the total peripheral resistance (30-60 percent) and arterial pressure (9-14 percent). Heart rate changed little. In the embolized rats, +dp/dt<sub>max</sub> and -dp/dt<sub>max</sub> tended to increase, if inconsistently. The elevated sensitivity of the cardiovascular system to the ouabain changes that effect very quickly to a toxic effect. Figures 1, references 13: 2 Russian, 11 Western.

### Complexes of $\beta$ -Glycyrrhizic Acid With Nonsteroid Antiinflammatory Agents as New Transport Forms

927C0468C Moscow *KHIMIKO-FARMATSEVTICHESKIY ZHURNAL* in Russian Vol 25 No 1, Feb 92 [manuscript submitted 3 Apr 90] pp 29-32

[Article by G. A. Tolstikov, L. A. Baltina, Yu. I. Murinov, V. A. Davydova, T. G. Tolstikova, A. I. Bondarev, F. S. Zarudiy, D. N. Lazareva, Institute of Chemistry, Bashkir Scientific Center, Ural Department, USSR Academy of Sciences; UDC 615.276.014.47:615.322:582:739].07]

[Abstract] Antiinflammatory agents widely used today in medical practice—aspirin and orthophene—have side effects that include, among other things, ulcerogenic action on the gastrointestinal tract and toxicity. Although such agents can be used in complexes with cyclodextrins to alleviate those side effects, there are other serious drawbacks to such combinations. The researchers here studied the combination of nonsteroid antiinflammatory agents and  $\beta$ -glycyrrhizic acid, the latter being the principal active ingredient in licorice root extract and having a high degree of antiinflammatory activity, without the side effects accompanying antiphlogistics. Molecular complexes of glycoside and aspirin and glycoside and orthophene (1:1 and 2:1 in each pair) were produced for study in outbred mice and rats. The complexes proved to have less of an irritating effect on gastric mucosa than did the nonsteroid antiinflammatory agents used alone. Degree of solubility was greater for the complexes, and they were found to be 2- to 9-fold less toxic than the aspirin or orthophene. The complexes exhibited antiinflammatory action that was roughly similar to that of the aspirin and orthophene alone, if not better at times when the dose was increased. The 2:1 orthophene complex, for example, kept edema induced by formalin inflammation down to roughly 30 percent (in a dose of 45 kg/mg), as opposed to 32 percent for the orthophene alone. Figures 1, references 14: 7 Russian, 4 Western, 3 Japanese.

### Properties of Microfiltration Membranes For High Degree of Purification of Drug Solutions

927C0468D Moscow *KHIMIKO-FARMATSEVTICHESKIY ZHURNAL* in Russian Vol 25 No 1, Feb 92 [manuscript submitted 19 Dec 89] pp 52-55

[Article by L. E. Yermakova, M. P. Sidorova, A. M. Gusynina, N. S. Snegireva, Leningrad University, All-Union Scientific Research Institute Medpolimer, Moscow; UDC 615.2/.3.014.24].012.8]

[Abstract] In light of the growing use of microfiltration in the production and study of drug solutions, the researchers here chose to study the structural and surface electrical characteristics of five types of membranes—two with a cellulose polymer matrix, one with a glass-fiber matrix, one with a nitrocellulose matrix, and one with an acetalcellulose matrix. The researchers concluded that for solution concentrations near 0.1 mol/l NaCl, the description of the mechanism of the process associated with microfiltration must take into account the charge and the potential of the membrane surface. The conclusion is significant in that, for the chemical-pharmaceutical industry and for blood-substitute production, solutions of that concentration are extremely important—the most widespread solvent for drugs is the saline solution that is a decimolar solution of NaCl in distilled water. Just such a salt composition exists in blood plasma preparations, most of the nutrient media for microorganisms, and other media associated with physiologically and biologically active solutions. Figures 2, references 5: Russian.

**Differences in Mechanisms of  $\beta$ -Acetyl-Digoxin, Strophanthin K, and Ouabain Effects**

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EKSPERIMENTALNOY BIOLOGII I MEDITSINY  
in Russian Vol 113 No 2, Feb 92 (manuscript received  
31 May 91) pp 146-149

[Article by N. V. Karsanov, G. V. Sukoyan, D. R. Tatulashvili, V. N. Karsanov, L. D. Mamulashvili, Republic Scientific Research Center for Medical Biophysics, Georgian Ministry of Health and Sanitation Department; Tbilisi State Medical Institute; UDC 612.054.4+615.015:536.7:513.172]

[Abstract] This research was devoted to demarcating the effect of calcium and glycosides on skinned muscle fibers (SMF) from 20 chinchilla rabbits (two-four kg). The study also involved determining some of the molecular pathways of the effects of  $\beta$ -acetyl-digoxin, strophanthin K, and ouabain on the system of contractile proteins in cardiomyocytes, especially with respect to calcium sensitivity and power conversion. The results showed that substituting the relaxing medium with the contractile medium (basically, the relaxing medium +  $\text{CaCl}_2$ ) moves the SMF from a resting condition to a condition of generating power. It was also demonstrated that when the SMF is pre-incubated with strophanthin K and  $\beta$ -acetyl-digoxin there is a considerable increase in the additional voltage and free energy from ATP hydrolysis. In addition, the data revealed that strophanthin K slows relaxation considerably in the reaction of actinomyosin complexes formed by a strong bond (AMCSB) to remove free calcium from the medium, in contrast to  $\beta$ -acetyl-digoxin and normal conditions. This indicates that there is a change in the binding strength of troponin C with calcium or the binding power of actin with myosin in AMCSB. The data also suggest that the pathway by which ouabain acts on SMF differs from strophanthin K and  $\beta$ -acetyl-digoxin *in vitro*. Ouabain does not alter the amount or rate of the following: voltage generated, the free energy from ATP hydrolysis of SMF, SMF relaxation as a result of removing free calcium, or trypsin proteolysis of myosin in the SMF. In conclusion, these findings serve as additional proof that ouabain alters the amount of energy generated by the system of contractile proteins only in the presence of an intact system of sarcoplasmic reticulum. Tables 1; references 12: 6 Russian, 6 Western.



### Modulation of Repopulation of Bone Marrow Colony-Forming Cells (CFC) by Recombinant Human IL-1B in Mice With Radiation and Burn Injuries

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pp 88-94

[Article by L.V. Alekseyeva, N.I. Izotova, S.A. Ketlinskiy, A.Ye. Pereverzev and A.S. Simbirtsev, Institute of Cytology, USSR Academy of Sciences; All-Union Scientific Research Institute of Highly Purified preparations, Leningrad; UDC 591.44:576.3:57.083:577.346]

[Abstract] Recombinant human IL-1 $\beta$  was tested in vivo and in vitro for its efficacy in preventing and reversing radiation- and thermally-induced damage in bone marrow cells. Analysis entailed determination of splenic colony formation in lethally-irradiated mice following intravenous injection with donor cells derived from syngeneic and allogenic systems after exposure of the donor animals or their bone marrow cells to various combinations of x-irradiation (3.06 or 6.12 Gy), 10 percent body burn (3 x 3 cm), or in vitro irradiation (3.06 Gy) and/or thermal shock (42°C for 10-20 min). The results showed that with irradiation IL-1 $\beta$  was effective in vivo and in vitro in the prophylactic and therapeutic modes. Therapeutic efficacy of IL-1 $\beta$  was also shown when radiation was combined with 10 percent body burn, but only with 3.06 Gy, and not when 6.12 Gy was employed. In in vitro studies IL-1 $\beta$  exhibited therapeutic potential only if added to the cells before the radiation + heat combination, but not after. These observations confirm previous reports on the immunotherapeutic possibilities of IL-1 $\beta$  in radiation and thermal injuries and suggest an approach to managing tissue incompatibility. Tables 3; references 23: 3 Russian.

### Modulating Effect of Kainic Acid on Release of Endogenous and Exogenous Glutamate From Rat Cerebral Cortex Synaptosomes

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MEMBRANY in Russian Vol 9 No 4, Apr 92  
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[Article by L. S. Solyakov, L. N. Petrova, O. A. Dranny, and S. O. Bachurin, Institute of Physiologically Active Substances, Russian Academy of Sciences, Chernogolovka, Moscow Oblast; UDC 577.175.82:577.352.465]

[Abstract] The modulating effect of kainate on processes of the K<sup>+</sup>-stimulated release of glutamate from cerebral cortex synaptosomes was investigated on male Wistar rats. The results showed that in the presence of kainic acid (50-250  $\mu$ M) the spontaneous release of glutamate increased by 76.2 percent in comparison with control animals. This is attributed to inhibition of the glutamate reverse capture system as well as stimulation of glutamate release by activating presynaptic kainate receptors. Investigation of the effect of kainic acid on the release of

endogenous glutamate revealed that the high affinity system of reverse glutamate capture is inhibited. In addition, it was shown that in the presence of 1 mM kainic acid the glutamate concentration in the incubation medium decreased to basal level three minutes after incubation began. The gradual increase in the glutamate concentration by 10 minutes is probably due to simultaneous blocking of the reverse capture system. Accordingly, the data suggest two possible explanations: 1. there is an alternative pathway distinct from the reverse capture system used for K<sup>+</sup>-stimulated glutamate release. 2. the K<sup>+</sup>-stimulated release of glutamate inhibited by kainate is mediated by an indirect effect on the transport system. In conclusion, kainic acid modulates the release of endogenous and exogenous glutamate from synaptosomes, increasing the spontaneous release and inhibiting K<sup>+</sup>-stimulated release. Finally, the inhibiting effect of kainic acid is possibly due to blockage of the influx of external K<sup>+</sup> into the nerve endings, while the increase in the spontaneous release is apparently due to inhibition of the high affinity system of glutamate reverse capture. Figures 2; tables 2; references 18: 1 Russian, 17 Western.

### The Intracellular Activity of Neuromediators

927C0514B Moscow USPEKHI SOVREMENNOY  
BIOLOGII in Russian Vol 111 No 2, Mar-Apr 92  
pp 265-272

[Article by T. M. Tretyak and L. V. Arkhipova, Institute of Experimental and Theoretical Biophysics of the Russian Academy of Sciences, Pushchino (Moscow Oblast); UDC 612.8.018]

[Text] The hypothesis is advanced that the catecholaminergic and serotonergic neuromediators not only play a role in synaptic transmission, but may also be inducers of intracellular synthesis. Evidence is presented of the direct interaction of neuromediators with DNA and other components of the cell nucleus. The data presented are of interest in connection with the investigations which are being widely carried out in the present time to clarify the mechanisms of the interaction of the molecules of inducers with the genetic apparatus.

### Introduction

A tendency has been noted at the present time toward a wider study of the biological activity of neuromediators than simply of the transmitters of the nerve impulse through the synaptic cleft. Investigations of the inducer role of mediators of varying kinds in embryogenesis of multicellular animals had their beginning more than ten years ago<sup>5, 16, 19</sup>. It has been demonstrated that the action of the neurotransmitters is effected at the early stages of cleavage and of the interblastomeric relationships. In ontogenesis the function of the neuromediators changes: Synaptic structures form, protein receptors appear, and the neuromediators begin to carry out the function of a connecting link between them to a significant degree. As the development of neurobiology has progressed, the picture of the molecular action of the

monoamine neuromediators has begun to be sketched: through a specific membrane protein regulated by guanylic nucleotide and through a system of enzymes that catalyzes the formation of intracellular transmitters. The intracellular transmitters, cyclic nucleotides or diacylglycerol, ultimately regulate the metabolic state of the cell by leading to a change in the level of phosphorylation<sup>20, 37, 39, 63</sup>. The notion arises in some instances, however, that an alternative pathway of the activity of the neuromediators exists. Thus, synchronous changes have not been found in the level of cAMP, the intensity of protein synthesis and the mitotic index<sup>52</sup> in cells of the blastema of the axolotl limb, incubated with norepinephrine or with antagonists of the adrenergic receptors. Nor was a relationship found between the presence of cAMP and the activity of RNA polymerase of the nuclei of the liver of rats subjected to electrostimulation of the hypothalamus<sup>24</sup>.

The objective of the present review is to try to discover the intracellular transmitter in question as well as the interaction of monoaminergic neuromediators with elements of the cell nucleus.

#### The Molecular Mechanism of the Intracellular Activity of Hormones

The activity of hormones may be regarded as an analog of the intracellular activity of the neuromediators. The mechanism of the intracellular activity of the hormones has been worked out quite extensively<sup>1, 7, 15, 42</sup>. And although the details of the specific interaction of various hormones with cytoplasmic and nuclear elements are currently being worked out, the basic schema proposed in 1972 by Khesin<sup>25</sup> remains timely. It is known that the cytoplasm and intracellular structures, including the nucleus, in addition to receptors located on the surface of the cell are equipped with intrareceptors that determine the "competence" of the cell for specific interaction with the effector<sup>25, 36</sup>. Many effectors, of which the steroid hormones are a typical example, combine in the cytoplasm with a receptor protein and in that form are transported into the nucleus, in which acceptor regions interacting with the hormone-receptor complex are found in the makeup of the chromatin. Such an interaction leads to an increase in the synthesizing capacity of chromatin and to the appearance of specific molecules of mRNA<sup>1, 39, 47, 56, 69</sup>. The molecular mechanism of the interaction of the steroid-receptor complex with the DNA of the cell nucleus remains unclear. It has been possible to demonstrate that the maximal binding of the complex with the DNA is accomplished in the presence of previously unknown low molecular weight factors<sup>30, 31</sup> that have been isolated from the cytoplasm and a homogenate of cell nuclei of the thymus by stepwise extraction using ammonium sulfate. Evidently a similar mechanism of the formation of the activity of steroids is represented in steroid-sensitive regions of the nervous system such as the ventromedial nucleus of the hypothalamus, the preoptic area, or the glucocorticoid-sensitive hippocampal zone<sup>57, 58</sup>. Information has also been published on the interdependence of the action of the

steroids and the catecholamines. Thus, 4-hydroxyestradiol-17 $\beta$  induced the accumulation of catecholamines in the developing brain of rats<sup>16</sup>, promoted the establishment of interstructural connections, and influenced integrative processes of the brain<sup>13</sup>. The receptors of the steroid hormones, androgens and estrogens, are found in the nuclei of the cells of such brain structures as the hypothalamus and amygdalae. The number of molecules of the receptors per nucleus is 10P20 thousand. The ultrastructural analysis of neurons of the ventromedial hypothalamus of rats subjected to the chronic effect of estradiol has revealed the presence in them of a luxuriant rough reticulum and dense vesicles, which usually is evidence of intense synthesis of macromolecules<sup>48</sup>.

The probable mechanism of interaction of steroid, thyroid, and certain polypeptide hormones with cell intrareceptors has been established<sup>7, 35, 49, 68</sup>. Receptors have been found in the nuclei of the cells of many tissues, having once united, with which the thyroid hormones induce the expression of the genes of competent tissues. Receptors of the thyroid hormones have also been found in the cell nuclei of neurons. It was found that the proportion of triiodothyronine is even greater than in other tissues in the nuclei of the cells of the neocortex of the receptors [as published]<sup>59, 70</sup>. The triiodothyronine receptor is extracted from chromatin by means of 0.4 M KCl. The molecular weight, 60 kilodaltons, has been established by the methods of gel filtration or centrifugation in a sucrose gradient. It belongs to the class of nonhistone proteins on the basis of its properties<sup>40, 71</sup>. The nuclear matrix and the nuclear membrane are furnished with receptors that possess a high affinity for triiodothyronine; this is manifested in a change in activity (specific binding number 86 nm) and in the number of binding sites (223 pM/mg of protein). The switching on of active synthesis following the decondensation of chromatin, which takes place as the result of the interaction of the chromatin receptor with triiodothyronine, induced subsequent activation of RNA polymerases which lasts 4-8 hours following the treatment of chromatin by the hormone<sup>34</sup>.

With the effect of thyroid hormones as well as steroids (see above) on the cell nucleus, a protein has been isolated from nuclear homogenates which intensifies the complementarity of the hormone-DNA conjugate<sup>29</sup>. Neither histone, nor serum protein, nor cytoplasmic proteins possess this property. The molecular weight of the nuclear protein is 65 kilodalton; it is sensitive to trypsin and unstable to heating.

The results of these experiments indicate nothing about the mechanism of transport of the hormone into the nucleus. Can the relatively small lipophilic molecule enter the nucleus by means of nonspecific diffusion, or is a special system of intracellular transport, consisting of protein enzymes and messenger molecules, operating in this case? Dexamethasone, for example, when added to PC 12 cells, induced an increase in the intracellular level

simultaneously of cAMP and phosphoinositol, and independently of the increase, cAMP as a metabolic factor induced growth and differentiation<sup>64</sup>.

The functional response of the nerve cell to the presence in it of triiodothyronine was expressed in a change in the activity of acetylcholinesterase, glutamate synthetase, and other enzyme markers of the metabolic state of neurons and glial cells<sup>32, 65</sup>.

Triiodothyronine promotes the increase in the number of GABAergic neurons in the telencephalon of rat embryos and does not alter the number of cholinergic neurons<sup>45</sup>. Triiodothyronine evoked some decrease in the incorporation of <sup>3</sup>H-thymidine in proliferating cells; however, this effect, which differs from the typical effect of a typical inhibitor of mitosis, cytosine arabinoside, can more likely be regarded as regulatory. Moreover, data have been obtained indicating that triiodothyronine participates in the processes of aging and of pathology that extends to neurons of the central nervous system<sup>36</sup>. On the other hand, insufficiency of thyroid hormones leads to a decrease in neurons of the neocortex and striatum of the content of RNA, as well as in the activity of acetylcholinesterase<sup>43, 51, 65</sup>.

Goldfein's article<sup>37</sup> on the interaction of cell nuclei isolated from the liver with the pancreatic hormone, insulin, appeared in 1976. The binding reaction was rapid, reversible, and directly proportional to the number of nuclei involved in the reaction. The nuclei, which were preliminarily incubated with unlabeled insulin became significantly less capable of reacting with the labeled insulin. Glucagon, somatotropin, and prolactin did not have an influence on the binding of radioactive insulin by the liver nuclei. Thus it was demonstrated in this study for the first time that not only steroid hormones, but certain polypeptide hormones can also penetrate the cell nucleus and perform the role of an inducer of the activity of the cell's genetic apparatus. The presence, on the other hand, in the cell nucleus of acceptor regions for a hormone leads to the notion of the existence of pathways in the reactions of the effector and the genome which are alternative to the intracellular messengers.

In fact it was recently confirmed that it was insulin itself and not the insulin receptor which accumulated in the nuclei of liver cells. This accumulation depended on the time of incubation of the cells with <sup>125</sup>I-insulin, the temperature of the reaction mixture, and the concentration of the hormone. It was demonstrated by means of electron immunochemistry that insulin in the cell nucleus is associated with heterochromatin, and only 1 percent of the radioactivity can be related to the radioactivity of <sup>125</sup>I-tyrosine, i.e., the insulin receptor.

The information enumerated regarding the intracellular activity of hormones prompted us to hypothesize that neuromediators in the cells of the nervous system may also fulfill the role of nonmediated inducers or regulators of the synthesizing activity of the genome. In other

words, a "quantum" of neuromediator is itself not only the material basis of the physiological response of the postsynaptic cell, but also switches on the genetic apparatus which produces a class of functionally necessary proteins<sup>21, 26, 28, 44</sup>.

### The Biological Effect of Neuromediators

It is the elucidation of the mechanisms of the establishment of synaptic transmission in the course of phylo- and ontogenesis which makes up the primary objective of the investigation of the participation of the neuromediators in preneural embryogenesis. It has been established in experiments on sea urchins and aplysia that the cell nucleus is the point of application of the activity of the neuromediators during the development of the embryos<sup>5, 6, 19</sup>. It has also been noted that antagonists of transmitters block the division of cells of the embryo<sup>14</sup>.

By using the developing retina of chicks as a model for the study of dopamine as a regulator of the growth of neurons, the authors of <sup>14</sup> found that 25 percent of the neurons respond to the micromolecular presence of dopamine by flattening of the cone of growth and by retraction of the dendrites.

The capacity of neuromediators to influence nuclear processes has also found confirmation in the results of an investigation of the transmitter influences on the transcription complex of hepatocytes<sup>10</sup>. In these experiments carbamylcholine was administered to adults rats, and six hours later the nuclei or chromatin, which served as the matrix of the RNA polymerase reaction, were isolated from the liver. The RNA polymerase of the rats which had received carbamylcholine possessed higher activity than the enzymes of the control animals. The activity of DNA-dependant RNA polymerase also increased in rats which had received norepinephrine; this was determined by the authors of <sup>46, 55</sup> on the basis of the intensity of the inclusion of <sup>14</sup>C-orotic acid into liver polysomes.

The addition of norepinephrine to a culture of rat hepatocytes stimulated DNA synthesis in them<sup>66</sup>. Since this effect of norepinephrine was inhibited by prazosin [as published], an antagonist of  $\alpha_1$ -receptors, but not by propranolol, an antagonist  $\beta$ -receptors, the inference was drawn that the influence of catecholamine on DNA synthesis was accomplished through the  $\alpha_1$ -receptors. This being the case, the activation of protein kinase C, the intensification of  $Ca_{2+}$  flux, and the subsequent cleavage of phosphoinositides can be expected. It is just such a chain of intracellular events that is governed by the engagement of the  $\alpha_1$ -receptors. The experimental verification of this postulate by means of the ionophore A-23187 (which stimulates  $Ca_{2+}$  flux) and of 12-O-tetradecanoylphorbol 13-acetate (an activator of protein kinase C) did not confirm the participation of this system in the process of the activation of DNA synthesis in hepatocytes.

Cruise and Michalopoulos<sup>33</sup> found that norepinephrine promotes the enhancement of the acceptance of <sup>3</sup>H-thymidine by rat hepatocytes when they incubated with

the monoamine not less than 12 hours. It is true that this influence appeared to the full extent in the presence of epidermal growth factor (EGF) via the  $\alpha_1$ -receptors and the EGF receptors. Membrane phospholipase  $A_2$  or guanine-binding proteins were activated simultaneously.

Another monoamine, serotonin (which belongs, as do the catecholamines, to the group of classical neuromediators), has been found in rapidly proliferating tissues. The administration of 5-hydroxytryptophan to mice with a generating liver (serotonin precursor) led to an increase in mitotic index of hepatocytes. A similar effect was observed when o-chlorpargyline, an inhibitor of monoamine oxidase, an enzyme which participates in the metabolism of serotonin, was administered. On the other hand, n-chlorophenylalanine and reserpine induced a decrease not only in the intracellular pool of serotonin, but in the mitotic index as well<sup>12</sup>.

Experiments involving tryptophan, in which rats were force-fed an increased amount of tryptophan, the only precursor of serotonin, and as a result of which the activity of RNA polymerases I and II in the chromatin of the animals' brain cells increased<sup>46</sup>, are indirect evidence in favor of an interaction of serotonin with the matrix. Serotonin has been found to be mitogenic for cultures of smooth muscle cells and fibroblasts: The addition of it to the medium in a dose of 10 mg per 100 g of body weight induced an increase in the incorporation of  $^{14}\text{C}$ -orotic acid into the RNA of hepatocytes<sup>54, 60</sup>. Antibodies to serotonin exerted the same effect as its inhibitors<sup>1, 11</sup>. Antiserum to serotonin inhibited and then even halted the cleavage of sea urchin embryos. This blockade was so enduring that neither perfusion, electrostimulation, nor the addition of normal serum to the medium removed the blocking influence of the antibodies.

A derivative of serotonin, 5-methoxytryptamine, is also active as a regulator of division in sea urchin embryos. Its secretion into the external medium was recorded at the end of the cycle of cell division<sup>53</sup>. A decrease in the level of serotonin in the organism under the influence of 5,7-dihydroxytryptamine (a neurotoxin of serotonergic neurons) led to the disappearance from electrophoregrams of two proteins of different brain structures of rats<sup>39</sup>. Possibly these are the same proteins which form serotonin-binding complexes which can be isolated from the cytosol of serotonergic neurons<sup>67</sup>.

A study in long-lived organotypic culture of the morpho-functional motility of the neocortex of mammals, which in natural conditions serve [as published] as the target for serotonergic innervation, has shown that the proliferation of glial cells is more active, the total growth zone and the thickness of the explant increase, the differentiation of neurons, the myelination of axons, and the formation of synapses accelerate in the presence of serotonin<sup>9</sup>. These experiments graphically reveal the presence of intracellular mechanisms of the biological activity of serotonin, in particular its interaction with the apparatus of cell division.

### The Influence of Catecholamines on the Processes of the Synthesis of Macromolecules in Nerve Tissue

The observation of the occurrence of disturbances in protein synthesis in patients receiving large doses of DOPA in order to correct neurological diseases is the probable impetus prompting the development of investigations of intracellular activity of neuromediators in the nerve cell. It has been found that when high doses of L-DOPA, D-DOPA, and  $\alpha$ -methyl-DOPA are administered, 43 percent of polysomes break down into monosomes, and the stores of S-adenosylmethionine in the brain are depleted; this underlies the decrease in the level of protein synthesis. In the presence of micromolar concentrations of dopamine 25 percent of neurons of the developing cellular tissue of chicks reacted with flattening of the cone of growth and retraction of dendrites<sup>41, 47</sup>.

However, it is unclear whether the intracellular activity of the monoamines is limited to an influence on the cytoplasmic synthesis of protein, or is its DNA also involved in the functional response of the cell? The incubation of DNA with norepinephrine and with  $\text{Cu}^{2+}$  has shown that DNA is "preferable" for DNA-dependant RNA polymerase<sup>61, 73</sup>. The authors explain the mechanism of this reaction by the occurrence of breaks in the phosphodiester bond with DNA treated with L-DOPA in the presence of  $\text{Cu}^{2+}$ . Experiments are known in which  $^3\text{H}$ -norepinephrine in a concentration of  $3.5 \times 10^{-9}$  M, injected into the lateral ventricles of the brain of rats, bound firmly with the proteins of chromatin and the karyoplasm<sup>4</sup>. The synthesis of two proteins with a molecular weight of 37 and 50 kilodalton in epiphyseal cells incubated with  $^3\text{H}$ -methionine is achieved under the control of norepinephrine. In addition, the synthesis of one of the proteins stopped in the presence of actinomycin D. Consequently, in this case as well, the action of catecholamine was realized at the level of the cell's genetic apparatus<sup>72</sup>.

An in vitro study of the possibility of the interaction of DNA with catecholamines and their derivatives has demonstrated that isomolar solutions of DNA-DOPA have an isobestic point with a stoichiometric ratio of the components of 0.5, i.e., two molecules of DOPA for one nucleotide at a set concentration of the interacting components<sup>23</sup>.

Published data and our own observations of the physicochemical interaction of DNA and DOPA suggest that DOPA and its structural analogs induce conformational changes in the secondary and tertiary structures<sup>3, 73</sup>. It has also been demonstrated that the adenylic nucleotides, ATP, ADP, and adenosine, are inclined to the formation of complexes with norepinephrine<sup>18</sup>. Thus, the possibility in principle of the interaction of the catecholamines with DNA and nucleotides has been corroborated.

It is difficult, however, to assert that the reaction of DNA with catecholamines in the cell takes place in an analogous manner. We can only attest that one hour following



the intraperitoneal administration of  $^3\text{H}$ -DOPA to rats more than 4 percent of the radioactivity entering the brain is found in the chromatin, from whence 70 percent of the bound amine can be extracted with 0.2-0.4 NaCl. The intraperitoneal administration of nonradioactive DOPA alters the capacity of the brain cells to assimilate labeled amino acids and RNA precursors<sup>22</sup>. Thus L-DOPA in a dose of 10-20 mg/kg of body weight increased the incorporation of  $^3\text{H}$ -leucine and  $^3\text{H}$ -uridine into nuclei of brain cells by 30-35 percent. In in vitro experiments the addition of L-DOPA to RNA synthesis reactions in a concentration of  $5 \times 10^{-9}$  M increased the matrix activity of chromatin by 15-20 percent, and preliminary incubation of chromatin with L-DOPA completely neutralized the action of an inhibitor, actinomycin D<sup>2</sup>.

We know of experiments in which  $^3\text{H}$ -norepinephrine accumulated in the nuclei of neurons when incubated with them for one hour<sup>4</sup>. When  $^3\text{H}$ -norepinephrine ( $3.5 \times 10^{-9}$  M) was introduced into the lateral ventricles of the brain, it bound intensely with chromatin and proteins of the karyoplasm. This result is of interest by reason of the possibility of the penetration of a mature neuromediator into nerve cells by means of so-called adsorption endocytosis<sup>8</sup>. It has been possible to simulate the intracellular activity of a neuromediator by transsynaptic impulse activation<sup>8, 28</sup>. It has been possible in experiments on the isolated cat cervical ganglion to increase the formation of tyrosine hydroxylase (an enzyme limiting the biosynthesis of catecholamines), which is accompanied by a three-fold increase in the amount of the corresponding mRNA. The denervation of the ganglion prevented the increase in the level of the mRNA which codes tyrosine hydroxylase during transsynaptic impulse activation. The mechanism of the increase in mRNA may in this instance be a dual one: It was, either due to acceleration of transcription, or as the result of the stabilization of already transcribed molecules, but by an impetus that induces a change in the amount of the neuromediator and a subsequent increase in the level of the activity of the genetic apparatus, that depolarization of the membranes, precisely, occurred.

The data obtained make it possible to assume that the neuromediators have a little-studied property, that of manifesting activity at the level of the cell nucleus. Such a situation probably arises during the plastic reorganization of already formed brain tissue, which requires the additional actuation of previously silent genes. The same process may be initiated in the presence of an increase in the local concentration of neuromediators as occurs in the pharmaceutical blockade of the monoamine oxidases.

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### **Met-Enkephalin Restores Self-Stimulation Behavior in Rabbits After Destruction of Hypothalamic Nuclei**

927C0518A Moscow *BYULLETEN EKSPERIMENTALNOY BIOLOGII I MEDITSINY* in Russian Vol 113 No 2, Feb 92 (manuscript received 17 Jul 91) pp 115-117

[Article by R. M. Saliyeva and L. V. Likhacheva, Emotion Physiology Laboratory, Normal Physiology Scientific Research Institute imeni P. K. Anokhin, USSR Academy of Medical Sciences, Moscow; UDC 612.826.4.089.62.014.46:[615.31:547.943:547.95]

[Abstract] The role of met-enkephalin in mechanisms of compensating for self-stimulation behavior after individual hypothalamic nuclei have been destroyed was researched in 51 male chinchilla rabbits (3-3.5 kg). The results of two series of experiments showed that the administration of met-enkephalin in doses of 0.1, 1, and 10 µg/kg depresses the self-stimulation frequency, with met-enkephalin in a dose of 0.1 µg/kg having the greatest effect in rabbits with a low baseline self-stimulation frequency. The depressing effect of met-enkephalin was displayed 46 minutes after it was injected into the lateral cerebral ventricles and peaked 20-45 min later. The findings also revealed that after the hypothalamic ventromedial nuclei were destroyed, the effect of met-enkephalin was more pronounced when it was administered to animals with a low baseline self-stimulation frequency. An evaluation of the data revealed that met-enkephalin alone depresses self-stimulation upon additional administration to the brain. At the same time, however, met-enkephalin also restores self-stimulation behavior that has been suppressed after various structures of the hypothalamus have been destroyed. It is believed that met-enkephalin receptors in other sections of the brain are still functional after local destruction of the hypothalamic structures; therefore, self-stimulation is restored in the lateral cerebral ventricles after the administration of met-enkephalin. Thus, these data are further proof that chemical compensation for lost functions of the brain is possible. Figures 2; references 13: 5 Russian, 8 Western.

### **Peptide Level Change in Rat Sensorimotor Cerebral Cortex in Response to Post-Stimulus Convulsive Discharges**

927C0518B Moscow *BYULLETEN EKSPERIMENTALNOY BIOLOGII I MEDITSINY* in Russian Vol 113 No 2, Feb 92 (manuscript received 17 Jul 91) pp 118-120

[Article by G. N. Kryzhanovskiy, V. K. Lutsenko, N. N. Khlebnikova, T. V. Goryacheva, and M. Yu. Karganov, General Pathology and Pathological Physiology Scientific Research Institute, USSR Academy of Medical Sciences, Moscow; UDC 612.825.015:547.96].014.42.08]

[Abstract] The involvement of peptides in the genesis of epileptic-like activity in the cerebral cortex, convulsive peak-wave type tracing discharges caused by rhythmic stimulation of the sensorimotor cortex, was investigated in mongrel male rats with a generator of pathologically amplified stimulation (GPAS). It was shown that the application of cortical extracts from the electrical stimulation zone (right hemisphere) and synaptic stimulation zone (left hemisphere) of rats with GPAS to the cortical surface of the same hemisphere sharply reduced the latency for the onset of the first convulsive tracing discharge. The results demonstrated that the pro-convulsive effect of extracts from both hemispheres of rats with GPAS cannot be attributed to a change in the level of met-enkephalin, leu-enkephalin, or somatostatin in the extracts. The fact that naloxone had no effect on the latency of the onset of tracing discharges casts doubt on the contribution of other opioid peptides on the onset of tracing discharges in the rat cerebral sensorimotor cortex. Judging by experimental data obtained with the use of naloxone, it appears that the opioid peptidergic system is not involved in the onset of convulsive activity caused by genetic factors in some animals and by focal epilepsy in man. Figures 1; tables 1; references 17: 5 Russian, 12 Western.

### **Antagonistic Properties of Tetra-Substituted Vasopressin Analog With Selective Anti-Diuretic Effect**

927C0518F Moscow *BYULLETEN EKSPERIMENTALNOY BIOLOGII I MEDITSINY* in Russian Vol 113 No 2, Feb 92 (manuscript received 04 Jun 91) pp 150-152

[Article by N. V. Myshlyakova, G. A. Afanasyeva, G. M. Strazda, O. S. Papsuyevich, N. V. Klusha, G. I. Chipens, Pharmacology and Peptide Chemistry Laboratory, Organic Synthesis Institute, Latvian Academy of Sciences; Biological Monitoring Laboratory, Experimental Factory, Organic Synthesis Institute, Latvian Academy of Sciences; UDC 547.466.1.057+547.269.3.04+615.357]

[Abstract] This paper presents the results of an investigation of a novel tetra-substituted analog of vasopressin. Experimental trials on albino rats (180-200 g) revealed that 0.05-500 µg/kg doses of the vasopressin analog had no effect on arterial pressure but exerted pronounced dose-dependent inhibition of the pressor effect of arginine-vasopressin. Investigation of the oxytocin activity of the vasopressin analog on an isolated

rat uterus revealed that in concentrations of  $10^{-9}$ - $10^{-5}$  M the substance has no effect on the smooth muscle. However, it does inhibit the myotropic effect of arginine-vasopressin. Finally, the anti-diuretic activity of the tetra-substituted vasopressin analog (1 ng/kg) was shown to be comparable to a 0.5 ng/kg dose of adiuretin, and thus displays selective anti-diuretic activity. This compound may find application as a pharmacological tool in investigation of the hormone-receptor interaction. Figures 3; references 4: Western.

**Morphometric Proof of Delta Sleep-Inducing Peptide Activation of Axosomatic Synapses**

927C0518K Moscow BYULLETEN  
EKSPERIMENTALNOY BIOLOGII I MEDITSINY  
in Russian Vol 113 No 2, Feb 92 (manuscript received  
16 Jul 91) pp 202-203

[Article by A. M. Mendzheritskiy, G. A. Kurayev, I. I. Mikhaleva, and P. E. Povilaytite, Neurocybernetics Scientific Research Institute, Rostov University; UDC 612.822.014.46:[6615.357:577.175.82]

[Abstract] The condition of the ultrastructure of axosomatic synapses in layers III-V of the neocortex was investigated in rats three and 24 hours after a single intraperitoneal injection of delta sleep-inducing peptide (12  $\mu$ g/100 g). Examination of the synapse ultrastructure at 15,000x magnification showed that DSIP activates the presynaptic endings in the bodies of the large pyramids in layers III-V of the rat sensorimotor cortex. Morphometric analysis of the plasmalemma of the pyramidal neurons in layers III-V at 3,000x magnification revealed an 11.2 percent increase in mean length three hours after DSIP administration, which returned to normal within 24 hours. The slight (10.7 percent) increase in the width of the synaptic fissure suggests activation of this type of synapse in the bodies of the pyramidal neurons under the influence of DSIP. In conclusion, the activation of axosomatic synapses correlates with an increase in the GABA level and slow-wave activity in the cerebral cortex hemispheres. Tables 1; references 4: Russian.

**Directions of the Activities at 'Ukrmedbioprom' Concern**

927C0461A Kiev FARMATSEVITYCHNYY ZHURNAL in Ukrainian No 2, Mar-Apr 92 pp 5-7; UDC 615.45

**[Text] Ukrainian Medical Industry in its Formative Process Editorial**

*Considering the fact that the quality of medical service to the population is related to drug production level, a new section was added to this journal covering the state of the development of Ukrainian Medical Industry. A selection of papers by the executives of the concern "Ukrmedbioprom" (Abbreviation for Ukrainian Bio-Medical Industry) covering the development of medical industry in Ukraine and the projections of future developments is being presented.*

**Directions of the Activities at "Ukrmedbioprom" Concern**

The Ukrainian concern devoted to the manufacture of medical and microbiological products, "Ukrmedbioprom," specializes in production of reagents for human and veterinary use. The production of the reagents is carried out on more than 30 chemical-pharmaceutical and biotechnological undertakings in Ukraine. In addition, this concern also includes four companies producing bacterial preparations; six companies involved in production of medical glass-ware; plants manufacturing medical products made from polymers; plants making technical equipment for the internal use; construction-assembly organizations servicing various branches of this concern; joint ventures developed with Vietnamese and Pakistani companies; the State Scientific Drug Center; the Scientific Research Institute "Syntez", two design-planning Institutes and an export-trade company "Biomed". The principal drug producers of this concern include the following Chemical-Pharmaceutical Production Associations (CPPA): in Kiev—"Darnytsya"; in Lviv—"Lvivfarm"; in Odessa—"Biotymulyator"; in Kharkiv—Pharmaceutical Company "Zdorovya", in Uman—Production Association "Vitaminy"; in Kharkiv—Chemical-Pharmaceutical Plant "Chervona Zirka" (Red Star); in Kiev—Stockholding Company "Farmak"; in Dnipropetrovske and Luhanske—Chemical-Pharmaceutical Plants; Production Association "Lubnykhimfarm"; Biochemical Production Association "Enzym"; in Kiev—Drug Production Plant, etc. These units produce around 600 medical preparations based on animal and plant starting materials, using organic, bioorganic and microbiological synthetic methods, as well as various biological products for the chemical, agricultural, food, and cosmetic industries. The overall production by these units is in excess of 2 billion karbovanets; around 40 million dollars worth of goods are being exported to all republics of the former Union and to ten foreign countries. The following new brand names entered the production line during 1991: aerosol "Leoxazol"—an anti-inflammatory reagent; Nitrogranulone and Phenigidine—cardiovascular preparations; Pheracine—an agent for purging of radioactive cesium; Aminolone—a

nootropic preparation; Flamine—granulated bile stimulating reagent for children; Cabamamide tablets for pediatric use; Litonide tablets for treatment of alcoholism; psychotropic reagent Amiridine; soporific agent for children—Nitrazepam in tablets, etc. The concern maintains close ties with categorical Scientific Research Institutes in Ukraine and other Republics of the former Union in the area of drug development and biotechnological preparations for various branches of the national economy. The scientific strength in the area of drug development is maintained by the concern through ties with the State Scientific Center of Drugs and with the Central Plant Laboratories (CPL). Five of these central laboratories work on synthesis of reagents; 11 subunits are involved in formulation and pre-clinical evaluation of these compounds; 13 subunits work on development of drug formulation and technical documentation required for their production, and five subunits concentrate on analytical methods, standardization and quality control documentation. Availability of the required specialized services staffed with qualified personnel and a core of modern instruments and equipment support this research effort starting at the synthesis of the reagents and terminating in submission of medical end-products for industrial production. The work is limited somewhat by the lack of animal breeding facilities. The planned construction of an animal facility at the State Scientific Drug Center will elevate drug development to the level of international standards, allowing complete preclinical evaluation of new drug candidates and of supportive chemical-pharmaceutical reagents in a much shorter time (within five years), thus accelerating the delivery of the required medicines to the population at large. The "Ukrmedbioprom" is in the process of negotiating a construction contract of an animal breeding facility at the Center site with the "Charles River" Company (USA) to the tune of about 2.8 million dollars; this will provide clean animal lines not only for the concern personnel, but also for other institutions in Ukraine. CPLs play an important role in development of the preparations produced by the individual units of the concern because they act as a liaison between the research components and the production line, providing specific working solutions developed by their plants. CPLs employ over 350 individuals. "Ukrmedbioprom" developed a number of programs. "The program for drug production based on material expected to be released during 1991-1995 by the component units of the concern" anticipates manufacturing the following drugs: salicylic acid, Dime-drol, Nitrazepam, Ameridine, Nitroxoline, Paracetamol, etc. "The 1992-1997 time frame program for manufacturing drug analogs of items purchased in the past from abroad" projects drug production that would adequately cover the needs of medical institutions in Ukraine and of the general population. "The Program for science and technology development during 1992-1996 period" projects development and production of the following pharmaco-therapeutic groups:

- cardiovascular drugs
- psychotropic drugs
- agents for treatment of alcoholism and addictions

- medicines for treatment of respiratory diseases
- antirheumatic, anti-gout, analgesic and fever reducing drugs
- anesthetics
- drugs for treatment of gastro-intestinal diseases
- antiallergic drugs
- immunomodulators
- radioprotectors and drugs to treat radiation diseases
- vitamins
- enzymes and antienzymic preparations
- drugs to correct metabolic processes
- special medications used in dermatology, venereal diseases, urology, and ophthalmology
- drugs to treat oncologic diseases
- reagents affecting metabolic processes
- diagnostic reagents
- medicinal plants
- supportive reagents
- medical preparations from polymers and other materials.

The principal scientific directions in the planning of work for the period 1992-1995 are:

- production of preparations from plant sources
- production of synthetic and semi-synthetic reagents
- production of supportive chemical-pharmaceutical reagents
- required to increase the effectiveness of the drugs
- basic research in development of new, original drugs, including pediatric drugs and drugs of prolonged action
- development of analytical and quality control methods for finished drugs
- development of biotechnology
- development of ecologically pure technological processes directed at improvement of the production of drugs and other principal medications.

In solving the drug production question we are obligated to assure their ecological purity. The ecological safety at the concern enterprises is still unsatisfactory. This leads to a task of developing technical processes which would minimize the levels of dangerous emissions. The National Scientific Drug Center works in this area and already has achieved concrete results. For example, the project on lowering emissions of dangerous substances into the atmosphere during the transport and vacuum evaporation led to a decrease of 150 tons of hexane, diethyl ether, ethanol, ethyl acetate emissions during production of Kaleflon, Vitamin A, Flamine, etc. A suggestion was made that the plants add an appendix to the regulation for the introduction of new easily controllable process parameters. The use of such parameters should lower by about 70 tons the emission of the following agents into the atmosphere: dichloroethane from the production of Splenine, methylene chloride from the production of Raunatine, carbon tetrachloride from the production of Silibore. Documentation was prepared for maximum permissible levels of the emissions of dangerous substances into the atmosphere for the Uman

Vitamin Factory and the Monastyrshchin Chemical-Pharmaceutical Plant. Methodology was developed for Kharkiv Pharmaceutical Company "Zdorovya" for quantitative determination of narcotic substances in the industrial effluent in connection with the production of ampules, and initial ecological data were published for 22 production processes at the All Union Chemical-Pharmaceutical Production Association "Darnytsya". Development and production of drugs for pediatric use are of a social-economical importance. The staff of the Scientific Center, while working on the development of new drugs for children, developed technical solutions permitting a decrease in the reactive material (in comparison to adult dosages) which resulted in much lower bacterial contamination of the medical form, higher bio-accessibility, greater safety and higher pharmacological activity. At this time the concern "Ukrmedbioprom" carries out an important work in organizing cooperation with other enterprises and foreign companies in production of sanitary-hygienic and therapeutic-prophylactic materials, biological additives for foods and cosmetic products, common development of the "know-how" for new drugs and improvement of those already in production. In this fashion, the entire activity of the structural subunits of "Ukrmedbioprom" concern is directed towards a rapid creation of contemporary medical industry in Ukraine.

#### On the Question of the Health of the Population of the Azerbaydzhani SSR

927C0472A Moscow SOVETSKOYE  
ZDRAVOOKHRANENIYE, in Russian No 10, Oct 91  
pp 32-34

[Article by R. M. Guseynov, Dep. Minister of Health of the Azerbaydzhani SSR; UDC 614.2 (479.24)]

[Text] The demographic situation which has taken shape in recent decades in the Azerbaydzhani SSR as well as the features of its development have posed a series of new socioeconomic and medical problems.

At the beginning of the 1960's the Azerbaydzhani SSR was distinguished among the union republics by a high level of natural growth in the population, which had reached 36 per 1000 in 1980, but which by 1988 had declined to 20.2.

The decrease in the natural growth was caused by a decline in the birth rate, which by 1988 had fallen to 26.9 births per 1000.

This fall-off was determined both by a change in the age structure and by a decline in the fertility of women of fertile age in all age groups.

A tendency towards a shift from families with many children to families with an average number of children was fully manifested in the republic as the result of the sharp decline in the birth rate. A decrease in the relative size of the contingent of third- and later-born children is



evidence of this. Thus, if this figure was 60.6 percent for the republic as a whole in 1960, in 1987 it had fallen to 32.5 percent.

The total mortality rate for the population remained practically unchanged in recent decades, and is less than 7 per 1000.

However, an unfavorable tendency of an increase in mortality for those 50 years old and older appears against the background of the stabilization of the mortality rate; this increase was governed by the so-called "diseases of old-age", i.e., neoplasms, diseases of the circulatory system and the respiratory organs. The highest relative proportion among the causes of death in 1960 was due to diseases of the circulatory system (21.4 percent), diseases of the respiratory organs (16.0 percent), neoplasms (9.8 percent), infectious and parasitic diseases (13.3 percent); i.e., about half the deaths (60.5 percent) were due to these diseases. In 1987 the relative proportion of mortality from these diseases were, respectively: 49.7; 14.3; 12.5; and 4.8 percent, i.e., 81.3 percent of all deaths.

The increase in mortality from diseases of the circulatory system as well as from neoplasms played the leading role in the increase in the relative proportion of deaths from these diseases. In 1960 the proportion of deaths from these causes was 74.8 percent in the urban population and 49.2 percent in the rural population; in the 1987 these figures were 81.7 and 80.9 percent, respectively. The latter attests to a sharp increase in mortality from these causes in rural areas, brought about by a deterioration in the ecological situation as a result of the chemization of agricultural production.

Azerbaijan holds first place in the country with respect to use of pesticides as calculated per 1 ha of area. In cotton- and vegetable-growing regions this use reaches 40 kg per 1 ha, while in vinicultural regions, it reaches as much as 183 kg.

Such unwise use of pesticides cannot fail to be reflected in the health of the population. As sociological research has shown, up to 68.7 percent of the total number of pregnancies in women employed in agricultural production ended in miscarriages.

A comparative comprehensive investigation carried out in the republic in two farms of the Agdashskiy district identified a highly characteristic pattern. The total morbidity rates for children up to six years of age in the zone of intense chemization (the "Uzbekistan") kolkhoz [collective farm] were found to be 4.6 times higher than in the zone of minimal chemization (the "Kavkaz" kolkhoz).

Undoubtedly, the level of material welfare is the basis of the deterioration of the population health indices. In 1987 the consumption of the national income per person in the Azerbaydzhani SSR was 974.8 rubles, i.e., it lagged behind the mean national level by 37.5 percent.

Although certain positive shifts in the level of capital investments in the development of public health have taken place since 1960, nonetheless the Azerbaijan SSR continues to occupy one of the last places among the union republics on the basis of its volume per 1000 inhabitants.

Capital investments for the construction of public health facilities have not been exploited fully for a long time; this is mainly due to the low level of the material-technical base of the building and repair organizations.

The level of current expenditures from the government budget targeted for public health development also remains low. Per capita expenditures were 16.3 rubles in the republic in 1960; 25.7 rubles in 1970; 34.4 rubles in 1980; 39.7 rubles in 1985; and 40.9 in 1987; i.e., they lagged behind mean national levels by 23.8-44.6 percent.

The intensive formation of the bed stock has, as a rule, gone on on the basis of modification and concentration, which has been reflected substantially in the qualitative side of its development and has led to a significant violation of sanitary standards (2.5 m<sup>2</sup> per one hospital bed).

Although the achievements of the initial stage of restructuring in the country have also been reflected positively in a number of indices which characterize public health development and the state of health of the republic's population, they have not led to serious changes. The further implementation of a complex of measures directed toward the improvement of socioeconomic and ecological conditions in the republic and the improvement of the population's health protection service are required.

It is necessary, in order to enhance the effectiveness of public health service management, to shift from quantitative to qualitative indices which will make it possible to compare genuinely the level of development of its material-technical service in various regions of the country. For example, in hospitals the bed-equipment level, defined as the ratio of the value of the equipment to the number of beds, and in outpatient-polyclinic institutions, the labor-equipment level (value of the equipment per one physician) can serve as such indices.

In contemporary conditions, when special attention is devoted to the development of the material-technical base of the public health system, its planning and the distribution of facilities must be based not only on the demographic potential, but also on the study of the geography of the causes of death and of morbidity as well, including the enlistment of the results of sociological investigations.

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### Infectious Diseases in the Driving Factors of Societal Health

927C0477A Alma-Ata ZDRAVOOKHRANENIYE  
KAZAKHSTANA in Russian No 11, Nov 91 pp 1-5

[Article by Ye. S. Belozеров, Alma-Ata Medical Institute; UDC 616.9:614.2]

[Text] Facing man today are such global problems as hunger, helminths, viruses, and ecology. Suffice it to say that one out of every five inhabitants on the planet is starving. Malthus was right: There are more people today than the Earth can feed. The unrestrained chemicalization, combined with the intense growth of industry, has given birth to serious ecological problems—harmful environmental factors affecting societal health. Many regions of the country, including Kazakhstan (Aral region, Ekibastuz, Ust-Kamenogorsk, Chimkent, Karaganda, and Aktau), are in a crisis situation in which anthropogenic factors are exceeding the potential and stability of the landscape. Anthropogenic stress is resulting in secondary immunological deficiency among the population, which is helping to elevate sensitivity to bacteria and viruses and is contributing to the growth of disease, including disease caused by pathogenic flora. For example, in Chernobyl, herpetic infection is growing, with a lethality of up to 80 percent. That same immunodeficiency is causing a growth in cytomegaloviral infection, in which pregnant women are giving birth to nonviable babies in half the cases, are having miscarriages in a third of the cases, and are bearing stillborn children in 5 percent of cases. Helminths are a constant companion of man, and all human populations are infected with them. In the Union, more than 40 million individuals have been invaded by them, which is 1.5-fold greater than the number of all individuals admitted to infectious hospitals. And the invasions are avitaminosis, mental retardation, and retarded growth. Viruses represent a serious problem. The number of viral infections is growing, and the number of diseases caused by viruses is increasing. They are new forms—AIDS, hemorrhagic fevers, delta viral hepatitis caused by the delta virus. They are also etiological interpretations of "old," long known diseases. There are more and more data pointing to the viral nature of rheumatoid arthritis, atherosclerosis, multiple sclerosis, and leukemia. According to the international classification, today there are 999 forms of human disease accounting for 30,000 named diseases, plus 2,500 infectious disease agents. The agents are bacteria and rickettsia (1,000), viruses (500), fungi (500), and helminths and protozoa (200). And although of the 30,000 named diseases, only 2,500 are considered infectious, scientific analysis indicates that one-third of the cases involving those 999 forms of human pathology have been proven to be or are felt to be of an infectious nature. Some scientists feel that 95 out of every 100 individuals who are admitted to a somatic hospital have a virus as a source of their disease. In addition, the existing system of statistics does not include under the

rubric of "infectious" many diseases that are truly infectious: acute respiratory viral infections [ORVI], bronchopulmonary diseases, chronic hepatitis, and cirrhosis of the liver. Paradoxically, it often happens that a contagious, infectious patient who is dangerous to those around him—such as someone with chronic hepatitis or cirrhosis of the liver or a child with pneumonia—is admitted to a somatic hospital, whereas a noninfectious patient is placed in an infectious hospital (brucellosis, erysipelas, etc.). According to statistical data, among the causes of death in Kazakhstan, diseases of the circulatory system account for 44 percent; tumors, 16 percent; diseases of the respiratory organs, 14 percent; traumas, 13 percent; diseases of the gastrointestinal tract, 5 percent; death associated with pregnancy or childbirth, 3.3 percent; and death from infectious disease, 3.2 percent. But in fact, scientific analysis clearly shows that one-third of the population dies from infectious disease. According to existing statistics, among all those who die from diseases included under the rubric "infectious," two-thirds are children under one year of age, and the proportion of infections in child mortality has increased threefold since the 1970's. Analysis of the causes of death from infectious diseases has shown that of those who died, 86.6 percent were children under one year of age. Among those, 40 percent dies of acute intestinal infection, 40 percent dies of sepsis, 9 percent dies of meningococcal infection, and 2 percent dies of viral hepatitis. In 40 percent of the cases, the child's death could have been prevented. In the last 10 years, death from sepsis has fallen threefold, and that frequently made diagnosis, especially among children, is eliciting doubt. At the same time, individuals in whom the diseases are caused by pathogenic microbes and viruses are becoming intensive-care patients today. There are around 100 microorganisms that cause pyoinflammatory disease. For example, every fourth of the country's inhabitants enters a hospital once a year, and pyoinflammatory disease develops in 50 million. Of the 20 billion rubles [R] lost every year in the country to infectious diseases, R1 billion is spent on purulent-septic diseases. That hospital-acquired infection is becoming a real scourge, because it develops in 5 percent of those admitted to the country's hospitals, and one in every 12 deaths among them is a result of that very infection. In the United States, we should note, more people die from sepsis than from all other infectious or parasitic diseases. The sepsis involves primarily staphylococcal infection, which is carried by 50 percent of medical workers; weakened patients and patients who have received hormones or radiation therapy are infected. Especially susceptible are children because their bodies synthesize primarily the IgM class of antibodies and only weakly synthesize IgG, which fights staphylococcus. The sepsis also involves salmonella, which has grown 20-fold as a result of nosocomial infection; the mortality rate among children under one from such infection has also grown 20-fold. Finally, the sepsis involves hepatitis B. For example, according to the data of some authors, 45 percent of those admitted to an infectious hospital for hepatitis A are infected there with hepatitis B. Hepatitis B is a

typically bloodborne infection, perhaps the most fatal of all those that exist today. Over the last 15 years, viral hepatitis B has grown in the country by seven-fold, and that is not merely because of better diagnosis. For the Union as a whole, among those admitted to hospitals for viral hepatitis, 86 percent are diagnosed as having hepatitis A and 14 percent are diagnosed as having hepatitis B. In places where the diagnosis of hepatitis is better organized, hepatitis A accounts for 62 percent, hepatitis B for 33 percent, and hepatitis non A/non B, 5 percent. A somewhat different picture exists for us in Kazakhstan (Figure 1).

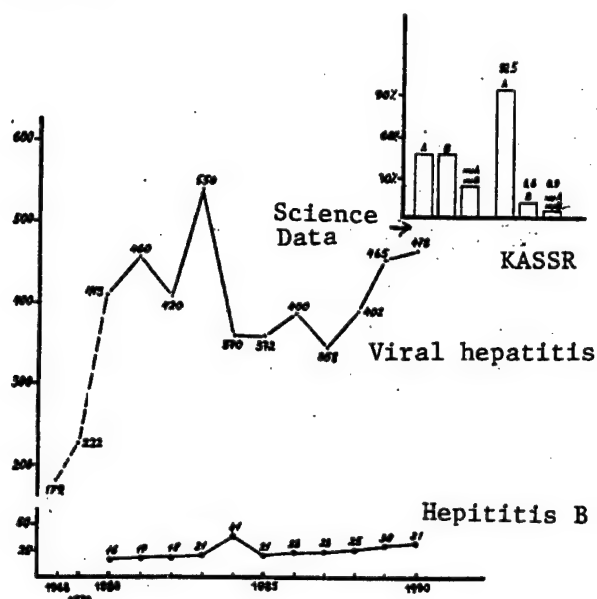


Fig. 1. Viral Hepatitis Morbidity in Kazakhstan

The danger of hepatitis B is growing, with every fifth infected individual (19 percent) becoming a chronic patient. According to WHO data, 5 percent of the Earth's population are carriers of hepatitis B, and that means nearly 300 million individuals. Of the infected adults, 5-10 percent become chronic carriers; of the infected newborns, 50 percent; of those infected in the womb, 70-90 percent. The solution to the problem is intensive immunization of those at risk. That measure is effective in 90-95 percent of cases before infection and in 75-80 percent of cases after contact with a hepatitis patient. Abroad today, some 30 million individuals have been inoculated. As already mentioned, acute intestinal infections in children account for 40 percent of the causes of death from infectious diseases. It must be borne in mind that we do not know the true state of morbidity, because, according to WHO data, there are 100 cases of unrecorded acute intestinal infection for every recorded case. Figure 2 presents the dynamics of the morbidity due to intestinal infections in the republic.

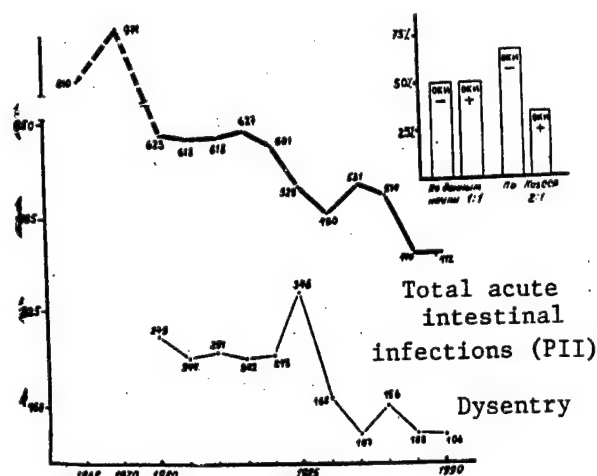


Fig. 2. Acute Intestinal Infections in Kazakhstan

In painstaking laboratory analyses done in Moscow among individuals ill with acute intestinal infection, the diagnosis in 36 percent was undetermined; salmonellosis was diagnosed in 27 percent, dysentery in 23 percent, and gastroenteritis of varying etiology in 4.5 percent. In Europe, campylobacteriosis [kampillo-bakterioz] is encountered more often than salmonellosis. One of the treatment tactics for acute intestinal infection is an excessive dosage of antibiotics or other drugs. Pediatricians suffer from that particularly. At the same time, WHO says that for diarrhea in children, the following are not indicated: sulfanilamides, neomycin or streptomycin, cardiac stimulants or steroids, spasmolytics or purgatives, kaolin or carbolene. If an enteritis syndrome is encountered in the clinic, rehydration and remineralization are indicated. Prevention of acute intestinal infection is exclusively the job of the government because acute intestinal infection is a health and social problem. It is felt today that infectious diseases need not be eliminated and that bringing morbidity due to them down to a nonepidemic level is the job of the health care sector. Controllable infectious illnesses require strict immunoprophylaxis. The issue of whether sick children should be inoculated arises, because they are usually the ones who get sick. Among the controllable infections, diphtheria and pertussis have grown two-fold in the country since 1985 because of improper policy regarding vaccination. For example, among those who contracted poliomyelitis, 41 percent had not been vaccinated and 37 percent did not have vaccination records. But for children to not get sick, 95 percent of them must be vaccinated. For now, though, that figure is no higher than 71 percent. Immunization has extended the lives of children two-fold. But not everything is clear with vaccinations. Of those infected with the polio virus, only 1 percent become ill; 40 percent of those injured have a titer of antibodies against tetanus that exceeds the protective level many times over. Children with T immunodeficiency cannot be immunized with live viral vaccine; children with B immunodeficiency cannot be

immunized with bacterial vaccines. Acute respiratory viral infections occupy the leading position both in terms of number of individuals ill with them and in terms of amount of material means expended on them (Figure 3).

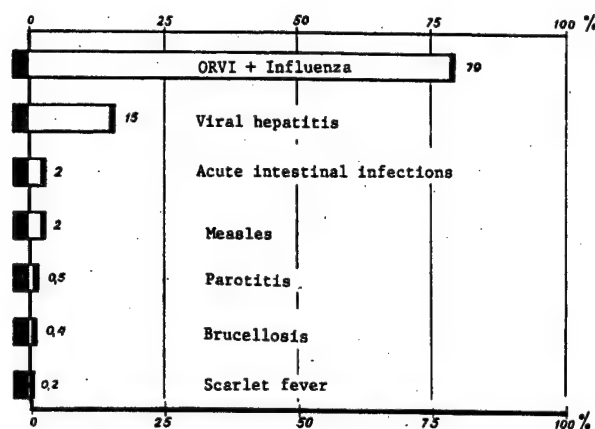


Fig. 3. Proportion of Losses in Structure of Infectious Disease in 1990

Nearly 200 viruses attack the respiratory tract, but on the whole, ORVI plus influenza take about 15 years off the natural human lifespan (Figure 4).

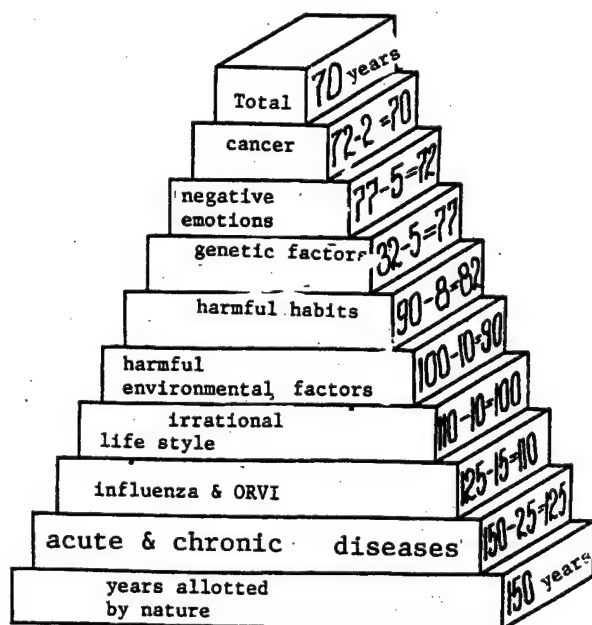


Figure 4. 'Contribution' of Different Factors to Reduction of Lifespan

But it is the virus that plays the determining role, and not the common cold, as many believe. To illustrate that, the Americans conducted an experiment: 100 students were wrapped in wet sheets and made cool; 100 other students went to movies, theaters, stadiums, and other peopled places where the risk of contracting ORVI was great. Respiratory infection was noted more often in the second group, because contact with individuals with a virus plays a dominant role. Among physicians in the republic, there is no single approach to diagnosing influenza and ORVI (Figure 5). The last problem that it

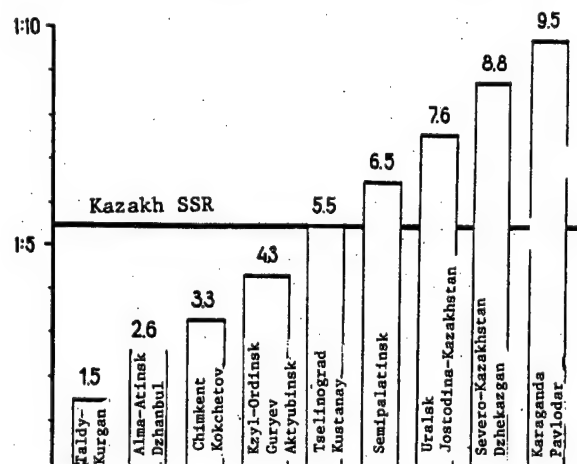


Figure 5. ORVI/Influenza Ratio in Republic (1990)

makes sense to talk about is drug therapy and the organization of rational therapy. In 1974, during an outbreak of paratyphus B, 22 percent of the residents of the settlement of Karsakpay became ill. Over a period of two weeks of intensive therapy with antibiotics in a [tolerance-inducing] regimen, two of 700 individuals died. After the introduction of the principle of treatment without the regimen (the principle is proven: the regimen is needed only when you do not have time to do anything else or when there is not anything else to do) and without antibiotics for most of those hospitalized, one individual died and that was on the first day that proper therapeutic care was being organized. Before 1972, treatment of brucellosis without vaccine was considered bad form. We excluded it from the arsenal of therapeutic means and got a better effect than when we used the vaccine. That is understandable: vaccine exacerbates the immunodeficiency of the II-III degree in terms of cell type that is typical for brucellosis. According to data provided by specialists, 95 percent of those who received antibiotics had no indications for them. The effect produced by boosting drug therapy (see the table) is not always adequate.

Amount of Drugs Per Patient and Duration of Stay in Bed

| Illness               | Years     | Amount of drugs | Average stay in bed |
|-----------------------|-----------|-----------------|---------------------|
| Cardiovascular system | 1965-     | 8.7 +/- 0.5     | 24.4 +/- 1.3        |
|                       | 1985      | 11.0 +/- 0.5    | 24.9 +/- 1.4        |
| Respiratory organs    | 1965-     | 8.4 +/- 0.4     | 18.9 +/- 1.8        |
|                       | 1985      | 13.8 +/- 0.8    | 20.7 +/- 1.0        |
| Digestive organs      | 1965-     | 6.5 +/- 0.6     | 15.6 +/- 1.1        |
|                       | 1985      | 9.7 +/- 0.5     | 25.1 +/- 0.7        |
| Locomotor apparatus   | 1980-1985 | 6.1 +/- 0.4     | 25.1 +/- 0.9        |
|                       | 1986-1990 | 6.6 +/- 0.3     | 26.0 +/- 0.8        |

The amount of drugs prescribed per patient per course of treatment is growing, and their effect on the human body is increasing. And it is not surprising that a tablet today is often more life-threatening than the surgeon's knife. In addition, the heavier drug loading is not producing recovery and is not shortening hospital stays (it often lengthens them). The number of side effects produced by the drugs on the body is also growing, which itself is lengthening bed stays. Moreover, according to data provided by U.S. specialists, three out of four who die in a hospital die from a disease and its severe course; one out of four dies from the treatment or from drug complications.

#### Diagnosis and Treatment of Extrapulmonary Tuberculosis

927C0477B Alma-Ata ZDRAVOOKHRANENIYE  
KAZAKHSTANA in Russian No 11, Nov 91 pp 6,7

[Article by T. A. Zhazykbayev, B. B. Babashev, Branch Tuberculosis Hospital, Dzhambul station, Oblast Osteotuberculosis Sanatorium Dzhambul; UDC 616.24—002.5]

[Text] The organization of the control of extrapulmonary tuberculosis, as well as the diagnosis and treatment of it, is effected by the oblast osteotuberculosis sanatorium Dzhambul, by the offices of the oblast tuberculosis dispensary, and by the branch tuberculosis hospital at Dzhambul station. At the oblast center, dispensary admission and active identification of tuberculosis patients is done by phthisiologist/osteopaths, oculists, and gynecologists. We do not have extrapulmonary tuberculosis specialists in the rayon tuberculosis dispensaries and tuberculosis offices, which is why since 1970 physicians (curators) of the oblast osteotuberculosis sanatorium who are responsible for group 5 dispensary rolls and consultation of risk groups in the polyclinics are attached to them.<sup>3</sup> The annual plans they put together are approved by the chief physician. According to the schedule, the curators go out every quarter to the rayons to which they are attached, where they conduct examinations of at-risk contingents: children in the "critical" period, individuals who have come in contact with bacillus-producers, patients with long-term, stubborn pains in the spine and joints, and patients with non-healing fistulas, chronic radiculitis, osteochondropathies, sugar diabetes, peptic ulcer and duodenal ulcer,

etc. Several organizational forms of timely identification and dispensary observation of those contingents have been developed and introduced. Together with the staff at the Kazakh Scientific Research Institute of Tuberculosis,<sup>2</sup> we prepared a procedural-information letter "Grouping of contingents of osteoarticular tuberculosis patients being served by the tuberculosis dispensary," which includes the new dispensary-rolls diagnostic group 5-0 and risk group 5-G, which were proposed by us. Those organizational forms and methods of early detection of tuberculosis of the bones and joints and of other forms of extrapulmonary tuberculosis in rural areas and the oversight of rayons by specialists have been introduced throughout the oblast. The new dispensary groups—5-0 (for individuals with extrapulmonary tuberculosis of questionable activity) and 5-G (for individuals who were transferred from subgroup 5-V, who were taken off the rolls, or who were diagnosed for the first time, or underwent spontaneous remission with pronounced residual changes) have been placed into the "Procedural instructions for grouping contingents of tuberculosis institutions."<sup>1</sup> The curators conduct seminars, conferences, and analyses of late diagnoses and check the outpatient treatment under monitoring and the adherence to the recommendations of the specialists. The curators have read 91 lectures, conducted six seminars and one conference, issued 20 health bulletins, and made 22 visits. Of the total number of new identified tuberculosis cases in 1987, osteoarticular tuberculosis accounted for 28.3 percent; tubercular lymphadenitis, which can be identified by means of biopsy only, 8.7 percent; tuberculosis of the eyes, 2.5 percent; and other forms of extrapulmonary tuberculosis, 5.0 percent. The morbidity associated with extrapulmonary forms of tuberculosis was 9.9 per 100,000 population in 1986 and 6.7 in 1987. The overall morbidity for tuberculosis in the oblast for those same periods was, however, 75.7 and 70.9. As a result of integrated measures for controlling tuberculosis, the outcomes of treatment have improved considerably: for type 1, 36 percent; type 2, 54 percent; type 3, 10 percent. Thus, thanks to the improvement of the material and cultural level of the population and to tuberculosis-control measures, morbidity due to extrapulmonary tuberculosis is on the decline in the oblast. Early detection and integrated treatment—which includes long-term chemotherapy, sanatorium and orthopedic care, surgical intervention, physiomechanical



therapy, and occupational training—are improving treatment results. New organizational forms (oversight) of early detection and the introduction of additional dispensary-roll groups have enabled ongoing dispensary observation of individuals with a questionable diagnosis or unspecified activity of osteoarticular tuberculosis, as well as individuals with residual effects on the locomotor system. All that has improved early diagnosis, treatment, and occupational rehabilitation of the indicated contingents.

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#### Diagnostic Center in Alma-Ata

927C0477C Alma-Ata ZDRAVOOKHRANENIYE  
KAZAKHSTANA in Russian No 11, Nov 91 pp 7-10

[Article by A. I. Izmalkov, KaSSR Ministry of Health;  
UDC 614.2:616—07]

[Text] The idea of creating the diagnostic center in Alma-Ata was that of the USSR Ministry of Health. It was expressed in the following manner: consolidate modern medical equipment under one reliable roof, inside walls no less reliable and consisting of highly skilled specialists. And call it the Alma-Ata Regional Diagnostic Center. And it will provide specialized care to residents sent by the treatment-prevention facilities of the capital and the oblast for functional, instrument, and laboratory tests that Other outpatient-polyclinic and hospital facilities cannot perform. Such a center was opened in 1988. It was the third such center in the Union, after the Moscow and Omsk centers. A model building was put up for it, with exemplary comforts like color televisions, good design, beautiful decorative vases, rugs, flower pots, and soft furniture. The doors had elegant placards, and the corridors were wide and filled with light. The newest, efficient equipment was placed in the offices and laboratories. A pneumoscope and a methatest (FRG) for ascertaining respiratory function; the Ultramark 6 (United States) for testing the cardiovascular system; the Vasoscan/vasoflow (Great Britain) for determining vascular tone in the upper and lower extremities and the brachiocephalic trunk; the Aloka 630 (Japan) for studying the organs of the abdominal cavity, the small pelvis, the lungs, and the thyroid and mammary glands; fibrogastrosopes (Olympus,

Japan); computer tomographs (Holland); X-ray machines (Hungary), and TUR [not further expanded] (GDR). Entire biochemical laboratories—Beckman and Abbott—were purchased in the United States. "Machine help" in making a diagnosis is exceptionally important, and the equipment acquired for hard currency was the latest word in medical technology. The equipment was purchased for \$5 million. It is being used to create a system of the greatest assistance in reaching an accurate diagnosis. The center has an information-dispatcher department; a laboratory department (clinical, biochemistry, clinical-immunological; and cytomorphological laboratories; functional, ultrasound diagnosis; and endoscopy divisions; plus a radiology division with computer tomography; a consultation division; a therapy division; a surgery division; a pediatrics division; and a psychosomatics division. Essentially, the center kept the divisions that any polyclinic would have. At the same time, it added new divisions, like the consultation division. It is there that we find the first children's diagnostics service—something that one might call ultra important in light of the levels of child morbidity and mortality in Kazakhstan. And another first, something the center is quite proud of, is a fundamentally new division—the psychosomatics division. How did it come about? Everyone knows that the body of any member of our society is subjected to stress both inside and outside the workplace. The stressors are things like mental and physical injury, blood loss, infection, irradiation, hunger, cold, and heat. The adverse factor that causes tension in the body may leave, but the "alarm" continues to sound. It threatens lives, and some of those who are stressed develop hypertension, others develop myocardial infarct, others sugar diabetes, and still others stomach or duodenal ulcers. In 30-75 percent of illnesses, they develop as a result of stress. Patients take drugs, but no healing results. Kilograms of drugs don't give any relief. So what is one to do? But the source is on the surface—stress is responsible for it all. Take away the stress, and the desired relief will not be kept away, like a guest at the door. That's what the center's psychosomatics service is involved with. Its representatives listen to the patient attentively, even if it takes an hour or two, and they prescribe hypnosis, or manual therapy, or acupuncture, or massage, or breathing exercises, or a sauna, or a bath. After the psychosomatics division came about in the center, the immense benefit it provides became obvious. Polyclinics are thinking about setting up psychosomatics offices because more and more so-called functionals are going to doctors without being sent. And there is even talk of setting up psychosomatics hospitals—a stressful life requires it. And the center is nurturing the idea of creating a small hospital (50 bed maximum). But not of the kind named above. A conventional hospital. The physicians in it would be involved with intensive care. The diet would be sensible, the treatment massive, and not with tablets (oh no! they're for home, for the family), but with intravenous administration of medications. The treatment would last days. And techniques from nontraditional medicine would be brought to the treatment, too. And of course, each

patient would receive individual care—without that it wouldn't even be worth thinking about the hospital! Within five to seven days, the patient would feel healthy—is that such a bad idea? In the meantime, patients are seen, diagnosis of disease at the prehospital stage is effective, hospital stays are shortened, opportunities to monitor the treatment process in an outpatient context are expanded, and consulting is of a high quality because highly skilled physicians of various kinds are enlisted to work in the center. Here, Professor A. A. Beremzhanov, a neurosurgery specialist, has an excellent reputation, as do urologist L. R. Minakova, pediatric nephrologist A. Sh. Ismagilova, gynecologist Z. Kh. Bakeyeva, and oncologist M. M. Akhmetov. And they're not the only ones. Working in the center at present are 143 physicians and 154 nurses, all of whom got there by competing for the positions, so that every specialist there ranks higher than the ordinary physician from an average polyclinic. And probably because the physicians are better qualified and the equipment is better, people are flocking to the center. And that's understandable: After the endless lines at the polyclinics, the cheerless little admissions windows, the shelves piled with outpatient charts, the diagnostic center seems like a miracle. And at this juncture, one can't help but say a few warm words about the director, Abay Kabytayevich Baygenzhin. He's been there since the very beginning of the center, and he helped pound and paint and equip the center, and he fought for a fundamentally new level of diagnosis. By nature, Abay Kabytayevich is an open fellow—everyone sees who he is right away. But that doesn't mean he's simple. He just doesn't hide anything about himself. His seriousness defines his life's work, a seriousness about everything—life and people. He knows full well that it's not honest people who are moving against the current, but officials who are holding on to the old times. And he doesn't sit around in his office. He's working, searching, taking others with him by dint of his enthusiasm and sincere impulse. And pervading everything he does is a captivating wisdom he has garnered from experience. He can't tolerate characterless people. One psychologist has said something like this: "A complete lack of character is a very contrary character." Abay Kabytayevich would agree with him. Baygenzhin loves his center—and how could it be otherwise?! Soon his brainchild will become an automated facility for preventive examinations: There will be displays, computers that "interview" the visitor, and test charts. Within minutes, a computer will give the visitor a detailed printout that he will take to the physician. Right now, that kind of examination takes three or four days. The advantages are obvious. And that will all happen in the near future. But right now, everything is going along the old, well-worn path. The number of visitors continues to grow. They can be seen from 8 in the morning until 9 at night on all four floors of the center. It's a volume of people that can be handled for now. In 1990, a total of 77,946 people passed through the registration office of the center. That was 20,530 more than did in

1989. There were 10,912 children. Residents of Alma-Ata Oblast made up 5.4 percent of those people; residents of Alma-Ata city, 93 percent; and residents of other oblasts of Kazakhstan, 1.6 percent. A total of 165,324 consultations were held and 964,212 tests performed. And one can't leave out a number like the percentage of guiding diagnoses different from final diagnoses. It was rather large. For example, in the pediatric division, it was 28.5 percent; in the surgery division, 25.4 percent; and in the therapy division, 24 percent. Also showing up in the work of the center is a modern, rather well-traced path like fee-based services. They are done with the help of the small enterprise Otan, which 7,000 patients have already gone through. Also well traced is the path characterizing economic-agreement principles. Economic agreements have been concluded with 50 leading Alma-Ata enterprises. Physician teams from the center screen patients, compile "medical health passports," make recommendations, ascertain how many people need active observation and how many need rehabilitation outside the hospital. The center, of course, has money. Physicians and nurses receive three times as much as others receive in any other polyclinic facility. All the staff members and their families are insured against illness and accidents. Their health is monitored by a trusted physician. The administration, understanding that the health of the staff is the wealth of the center, pays for athletic fields and swimming pools for them every year. Thanks to all that, morbidity among the staff members has dropped sharply. What was said above about the medical facility, which opened three years ago, is something from the future for many medical professionals. But what must happen for others tomorrow, began, in a manner of speaking, yesterday for the staff of the Alma-Ata center and is being implemented successfully today.

### Serodiagnosis of HIV Infection

927C0477E Alma-Ata ZDRAVOOKHRANENIYE  
KAZAKHSTANA in Russian No 11, Nov 91 pp 24-25

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[Text] An important aspect of the seroepidemiological diagnosis of HIV infection is the correct interpretation of the results received in the testing of the blood sera of donors and high-risk contingents in enzyme immunoassay (EIA). That stems from the fact that not only those who get a positive result in immunoblotting are placed on the dispensary rolls, but also those who get a positive result in EIA when a second portion of the serum is tested three times and immunoblotting is negative. Ambiguous results have been obtained when sera are tested for antibodies to HIV with the various domestic test systems that have been introduced into practice in the health care sector. That is why we decided to conduct simultaneous testing of sera with all the test

systems available. For the work, two sera containing antibodies to HIV (Nos. 1 and 2) were chosen. AIDS laboratories provided 30 blood serum samples from various oblasts of Kazakhstan (Nos. 3-32). According to the data of those laboratories, the presence of HIV antibodies was established with at least three tests in EIA of the second portions of the sera. In addition, 58 serum samples were taken from newly diagnosed individuals. Testing in indirect EIA was done with test systems from the following manufacturers: USSR Ministry of Medical Industry NPO Antigen, HIV and recombinant HIV; USSR Ministry of Medical Industry NPO Vektor, HIV and recombinant HIV; USSR Ministry of Medical Industry Pasteur Institute, recombinant HIV; and joint Soviet-Swiss DIAplus, recombinant HIV. The EIA results were evaluated on an MR-700 Seidel EIA photometer at a wavelength of 490 nm. Sera identified as positive were confirmed with immunoblotting. The immunoblotting test systems used were an experimental test system made by the NPO Vektor and the Western Blot HIV-1 test system made by DuPont (United States). The setup of the tests and the recording of the results were done in compliance with the instructions attached to the test-system kits. Thirty-two of the 90 sera tested were positive in various test systems. Results were positive with all six test systems in five cases, with three test systems in four cases, with two test systems in seven cases, and with one test system in 16 cases. In two repeat rounds, differences showed up among the sera that were positive with one or two test systems. In the first and second sera, the titer of antibodies appeared to be 1:800 and 1:1600, respectively. In all the other positive sera, it did not exceed 1:100. The magnitude of those extinctions exceeded the Cutoff 1.5- to 4-fold. All the sera that were positive three times with one or with all the test systems were entered in the confirmatory immunoblotting test (repeat tests of some of the sera in immunoblotting were done at the Gamaleya Institute, in the laboratory of Prof. V. I. Vasilyeva). In two of the sera positive with all the test systems, antibodies were identified to specific HIV proteins. In two others, reactivity to similar proteins p66, p51/55, dp41, and p24 was found in immunoblotting. In one of those five sera, no antibodies were identified. Of the four positive with three test systems, one serum was negative in immunoblotting. In three, reactivity to proteins p66 and p24 was recorded. Results were negative with the remaining 26 sera in immunoblotting. The greatest number of false positives in EIA and negatives in immunoblotting were produced with the test systems of NPO Vektor (recombinant HIV, 22 of 30) and the Leningrad Pasteur Institute (20 of 30). In a one-year observation of the individuals in whose sera antibodies to HIV proteins were identified (Nos. 5, 8, 11, 14, 25, and 45)—not counting the HIV-positive sera Nos. 1 and 2—there was no appearance of antibodies to either surface proteins or other structural HIV proteins. In three sera (Nos. 5, 8, and 45), reactivity disappeared completely; whereas in No. 25, reactivity to p24 and p51/55 remained. In Kazakhstan, 320 individuals have been identified with such reactivity. That amounts to 0.016 percent of the number of individuals

tested. Meanwhile, the data obtained and the unpredictability of the behavior of people taken in those instances on the dispensary rolls, requires a reexamination of our positions on dispensary observation. In light of the fact that domestic systems are not very advanced, especially those with recombinant virus, it would be best to take individuals on the dispensary rolls not after a positive result is obtained in EIA in practical laboratories, but after immunoblotting results are obtained. Otherwise, the identification of individuals whose sera were positive in EIA could be considered a matter of chance that will require taking individuals on the dispensary rolls who in fact do not have antibodies to HIV.

### Conclusions

1. The research conducted has shown the need to test initially positive sera again in at least two different EIA test systems.
2. The testing requires that every laboratory that does primary screening of sera always have a set of test systems that contains, for antibodies, both recombinant HIV and purified lysate of HIV-infected cells.
3. Individuals should be taken on the dispensary rolls as HIV-infected not after a positive result in EIA (two of three, or three of three repeat tests), but only after those sera are tested in immunoblotting and after identification of reactivity to at least one of the proteins analogous to HIV proteins.

### Training Instructors and Nursing Personnel in the Prevention and Control of HIV/AIDS

927C0477F Alma-Ata ZDRAVOOKHRANENIYE  
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[Text] In April 1987, the International Council of Nurses and WHO developed a joint declaration on AIDS that identified the rights and duties of mid-level medical personnel who care for patients infected with HIV and for AIDS patients. Of paramount significance in the prevention of HIV/AIDS is the training of personnel. Nurses and obstetrics personnel, through preventive health education, can affect not only the quality of the medical care provided for those infected with HIV, but also the dimensions of the epidemic. To do that, they must be trained to perform active educational work among personnel, patients, and the population and to render care to those suffering with the disease. Recognizing the urgent need to train mid-level personnel in this matter, our WHO center organized a seminar called "The Activity of the Nurse in the Prevention and Control of HIV/AIDS" and, together with WHO experts, conducted it in November 1990. For one week, chief

nurses from large treatment-prevention facilities, medical school instructors, and staff members of centers for the prevention and control of AIDS from the republics of Central Asia and Kazakhstan were able to learn of the newest data about AIDS. Theoretical and practical knowledge and skills in the prevention of HIV infection were learned, and special plans of action to control HIV infection and to provide nursing care were developed. The basis for the seminar were WHO-developed procedural materials: "Manual for Nursing Care for Patients with HIV Infection and for AIDS Patients," "Preventing the Transmission of HIV in Medical Facilities," and "Teaching Modules for Basic Nurse and Obstetrics Personnel Training in the Prevention of HIV Infection and the Control of It." They were prepared by staff members of our WHO center. We will talk in detail about the last manual, which is a teaching program for training nurses and obstetrics personnel. It consists of 10 module exercises that make it possible to set up intragroup contact among the students, develop specific training skills, identify priorities among problems, and find a way to solve the problems. The first module—"The Transmission and Epidemiology of HIV/AIDS"—makes it possible to train the students to use their own knowledge of the epidemiology of infection and to prevent the spread of the infection. That is the first step in the training of nurses to be informed professionals. They must know how to sense and understand the anxiety and alarm among individuals and in the society as a whole with regard to HIV-infected individuals, they must be able to explain how HIV infection is transmitted, and they must have an idea of the role they play in preventing the spread of the infection. They should also be aware of existing services and resources and local demographic data, in order to be able to render the necessary educational and advisory assistance to those who need it. The general purpose of the second module—"HIV Infection"—is to train students in the identification of the clinical signs of the infection and to discuss the question of the advisability of testing for HIV antibodies. Here, the program focuses on the disease process, a description of the clinical picture associated with HIV infection, and the differences between HIV infection and the diagnosis of AIDS. Familiarity with this section makes it possible to formulate among the students the bases of knowledge and skills for training and advising other individuals regarding the disease itself and regarding supportive care, practical measures in the prevention of HIV infection, and performance of the test for HIV antibodies. At this stage, they will study the immune system and the effects of HIV on it, the clinical manifestations of symptomatic HIV infection, will describe the test for HIV antibodies, and will discuss its aims, consequences, and limitations. The third module—"The Effect of HIV on Individuals and Society"—examines the issues associated with the reaction of society to the AIDS epidemic, which, as we know, elicits a very strong emotional response and fear. The behavior of individuals and population groups is affected by their sexual orientation, involvement with intravenous drug use, fear of infection, the torturous process of dying, religious and moral

convictions, the level of medical assistance, and socioeconomic conditions. Upon completion of the study of the materials of this module, the role of the nurse will be defined more clearly as a linking component in the local actions of society in response to the epidemic, as will the effect of HIV infection on individuals. The fourth module—"The Prevention of the Transmission of HIV in Medical Institutions"—is devoted to general precautionary measures that have been developed in accordance with WHO recommendations. Treatment facilities need to revise their policies in terms of making stricter requirements for and control of procedures in order to prevent the transmission of HIV within their own walls. To prevent that, the possible ways the infection is spread and the potential level of risk must be known, as well as the actions that must be taken in the event of an accidental outbreak of the infection. Students learn all that, acquiring the skills to prevent the transmission of HIV in hospitals and polyclinics and alternative procedures. The next module—"Teaching Patients How to Prevent the Transmission of HIV"—is devoted to ways of disseminating information on the prevention of HIV/AIDS. The nurse must become one of the sources for that kind of information, since every patient must know that. Even more important is her ability to help the individual to change his lifestyle and sexual behavior. Specific skills are needed for rendering that kind of consultation. The program of that module calls for teaching nurses how to provide consultation assistance to individuals in order to change their behavior, what the tactics are for effective education of the public in the prevention of the spread of HIV, how to explain how intravenous drug use puts one at risk for HIV infection, and what the measures are for preventing HIV infection. The sixth module is devoted to familiarizing nurses with the practice of folk healers. The equipment they use in tattooing, for example, can be a source of the spread of HIV. The nurse should have a knowledge of all types of instruments for puncturing the skin and how they can be replaced with safe alternatives; the nurse must also familiarize folk healers with methods for sterilizing their instruments. The program of the seventh module is devoted to nursing care of adult patients with symptomatic HIV infection or with AIDS. In mastering the program, the nurse must learn how to identify the typical changes that occur in the physical condition in symptomatic HIV infection. In addition, the nurse must learn how to identify opportunistic diseases associated with AIDS, how to manage a patient who can be treated and cared for in the home, and how to help such patients in solving physical, financial, social, and other types of problems. Issues associated with care for children of breast-feeding age or a little older who have symptomatic HIV infection are examined in the lessons of the eighth module. The diagnostic criteria and manifestations of disease in children are different from those in adults. Knowledge of those differences enables the nurse to correctly assess a situation. To be able to do that, she must learn to identify the signs and clinical characteristics of symptomatic HIV infection and AIDS among children, distinguish their course from other diseases,



and use diagnostic criteria to identify it among children. No less important is the ability to assess the capabilities and opportunities of family members to care for the sick child and the ability to put together a plan of diagnostic care of the diagnosed and identified patients on the basis of accepted standards and available resources. The ninth module—"HIV Infection Among Pregnant Women"—teaches about the potential danger of HIV infection to women planning a pregnancy, to pregnant women, and to women in the perinatal period. Also examined are questions associated with the special risk to the individuals who assist in the birthing. The nurse learns precautionary measures to be taken during the birthing that make it possible to prevent the transmission of HIV from the infected mother to medical personnel and the child. The final module examines questions associated with the care of AIDS patients in the terminal stage and care of individuals who have symptomatic HIV infection. The job of the nurse is to keep the patient as comfortable as possible and to show compassion, charity, and understanding to the patient and to those close to the patient. In the final analysis, the student will be able to meet the needs of HIV-infected individuals in the terminal stage, put together the concept of palliative treatment (as opposed to therapeutic treatment), and determine the role of the nurse or obstetrics personnel in providing that treatment to AIDS patients or individuals with symptomatic HIV infection. Unfortunately, the situation with AIDS is bad not only for the country as a whole, but is also bad in the republic: six territorial foci of HIV infection have already been identified. Against that backdrop, attention needs to be focused on health education and on training of health care personnel. In our view, the teaching modules on the prevention of HIV infection and the control of it are very timely. They will enable nurses, obstetrics personnel, and doctor's assistants to define their roles in the prevention of this menacing infection.

### The Burn Service of Russia

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pp 44-45

[Article by E. Panova, under the rubric "News From the Ministries and Departments"]

[Text] At one of the sessions of the board of the RSFSR Ministry of Health, the question of the improvement of specialized medical care for patients with burns was examined. At present in the republic are 3,858 burn beds, and 71 specialized divisions have been opened—including five children's divisions—where medical care for burn victims is rendered by nearly 400 specialists; postgraduate medical training of physicians is conducted at the republic burn center in the Nizhegorodskiy Scientific Research Institute of Traumatology and Orthopedics. Plans call for training to get under way at the USSR Ministry of Health All-Union Children's Burn Center and at the thermal burn division of the faculty for advanced training of physicians at the Nizhegorodskiy Medical Institute.

A fundamentally new level of medical care has resulted from the introduction of active surgical tactics and the open, dressing-free technique for the treatment of patients with deep, extensive burns, from the use of reticular skin transplants, chemical and enzymatic necrolysis, and the adjustment of protein and carbohydrate metabolism.

In addition, the growth in burn traumas, associated with the accidents and other unusual events that have been increasing in recent years and the high level of morbidity with temporary loss of ability to work and disability as a result of burn trauma require a solution of a number of problems associated with the further improvement of this type of specialized medical care. In 1990, the number of individuals sustaining burns in the republic was 652,000, which included 135,000 children, i.e., 441 cases per 100,000 population (in the USSR, it was 384 cases). Every year, more than 25,000 people die of burns, 5,500 of which are children (17/100,000 population).

The number of burn beds—0.26 per 10,000 population, when the norm is 0.4—enables hospitalization of only 22.8 percent of patients, of which one-third are children who need specialized treatment.

About 17 percent of the burn beds are in surgical or trauma divisions, where there is no financing, medical equipment, or medications specifically for the needs and features of treatment of burn patients.

Treatment-prevention facilities do not have enough dermatomes (only 10 percent of what is needed) or atherapeutic devices (29.5 percent), and they are poorly supplied with blood substitutes, blood protein preparations, broad-spectrum antibiotics, antiseptics, and hormonal preparations. Unresolved is the question associated with the domestic production of special beds and air mattresses or the purchase of them abroad.

The lack of adherence to triage during evacuation and treatment is leading to inefficient distribution of patients in terms of severity of burn trauma and is having a negative effect on treatment outcomes.

The quality of treatment and care is being lowered by the inadequate development of the network of specialized children's divisions and by the lack of pediatricians and pediatric burn-treatment specialists in the burn divisions, as well as by the absence of conditions that would enable the relatives of the victims to stay in the divisions.

Because of the lack of resuscitation units and intensive care units in the burn divisions (30 percent of the patients have severe burn trauma), intensive treatment with infusion of medications cannot be performed as fully as it should be. That is leading to the development of complications and is having a negative effect on the outcome of the illnesses.



Outpatient-polyclinic care for burn patients is not properly set up, nor is their dispensary observation or rehabilitation with care like sanatorium care or reconstructive-restorative treatment.

The development of the burn service is being held back by inadequate financing of the treatment-diagnosis process. In the RSFSR, from 300 to 1,700 rubles [R] are spent on one course of treatment; whereas, according to the data of the republic burn center, that spending should be R1,500-18,000.

The intense work, the considerable mental and emotional aspects of the work, and the elevated level of infectious-allergic illness among burn division staff members promotes a high turnover rate among personnel (more than 30 percent, on average) and inadequate staffing of burn divisions with physicians and mid-level and junior medical personnel.

There is still no training at burn divisions of republic, kray, or oblast hospitals of surgeons, traumatologists, anesthesiologist/resuscitation specialists, or physicians of the emergency medical service and emergency airlift service in matters of burn treatment. Researchers are devoting too little attention to "thermal trauma." Only four institutes in the republic do research in that area.

The RSFSR Ministry of Health has adopted a number of emergency measures to eliminate the inadequacies in the organization of medical care for individuals with burns and associated aftereffects and to further develop and improve that care. Procedural instructions that include standards and volumes of medical care for burn patients in various stages of evacuation and treatment have been approved. Positions have been taken on republic, inter-territorial, and oblast (kray, municipal) burn centers; on the children's burn division; and on the burn center (or division) resuscitation and intensive care division (or unit). Staff norms have been introduced; the structure of republic, interterritorial, and oblast burn centers (and divisions) has been developed; and a list of special equipment and instruments, medications and dressings, and blood and its preparations has been approved. Plans for 1991-1995 have been drawn up for raising the skills of specialists at the republic burn center.

The RSFSR Ministry of Health Nizhegorodskiy Scientific Research Institute of Traumatology and Orthopedics (director, Prof. V. Azolov) has been named the head consultation/treatment, teaching (postgraduate training), procedural facility for burn trauma among adults and children in RSFSR. It has been decided that interterritorial burn centers for adults and children will be created in 1991-1992. The causes of burn trauma need to be analyzed, as does the state of specialized medical care for burn patients (adults and children), and a long-term, comprehensive program needs to be developed for growth and improvement of organization, planning, and financing in the context of the new economic mechanism in health care.

It has been decided that, as priority measures for improving the medical care for adults and children suffering from burns, burn divisions with 40 or more beds will be set up by 1993 in republic, kray, oblast, and general city hospitals in accordance with the needs of the population for that type of specialized medical care. In administrative territories with a population of over 2 million, children's burn divisions that provide 0.15 bed per 10,000 population will be opened. The new services will execute the principles of triage and treatment on the basis of standards that provide for the optimal volume of medical care to burn-trauma patients; they will organize training of surgeons, traumatologists, anesthesiologist/resuscitation specialists, pediatricians from city and central rayon hospitals, and physicians from outpatient-polyclinic facilities of the emergency medical service and the emergency airlift service in matters involving how to render medical care to adult and child burn victims during the various stages of medical evacuation. Restorative treatment of children with burn trauma should be done at children's orthopedic sanatoria.

The chief physicians of treatment-prevention facilities that have burn divisions have been commissioned with the following duties: to organize in 1991-1992 round-the-clock emergency care for burn patients; to outfit burn-division resuscitation/intensive care units or divisions (after staffing them with specialists), day hospitals for rendering medical care to patients with limited burns and burns that are healing, separate operating rooms, if necessary, for performing reconstructive-restorative and plastic-surgery operations, and children's wards and isolation wards for treating intercurrent infections; and also to create conditions that will enable the mothers to stay in burn divisions and care for their children.

Special instructions have been given to the officials of the Farmatsiya production associations and the Chief Administration Rosmedtekhnika, to the scientific research institutes, to the rectors of medical institutes, and to the representatives of other subdivisions of the RSFSR Ministry of Health.

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#### **Activity of Health Care Departments in Emergency Situations**

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[Article by Prof. V. I. Talapin, I. Ya. Zhogalskiy, Belorussian Scientific Research Health-Hygiene Institute; UDC 614.7/.8(476)]

[Text] Emergency situations have occurred rather frequently in recent years in the republic. The Chernobyl tragedy, the cyanide leak at the Polimir [as published] Production Association, the ethyl mercaptan leak at the Grodno Gas-Filling Station, the sulfuric acid leak at the Minsk Tovarnyy station, the diesel fuel leak from the petroleum-products pipeline between Molodechno and

Novopolotsk, the fire at the toxic-chemical burial site in Bretsk Oblast, the dozens of daily highway transport accidents and fires—that's far from a complete list. As we know, the effectiveness of man's influence on the course of events depends largely on the depth of understanding of the causes of the phenomena that occur and the methodology associated with the training of health care departments to deal with the emergency circumstances.

In the opinion of those who take part in the response to accidents and disasters, as well as of researchers, examination of rescuers—including medical workers who work in extreme conditions for six to eight hours at a stretch—reveals substantial changes that affect their efficiency. Seventy-four percent of those examined developed obsessive ideas; 80 percent exhibited signs of posttraumatic stress response, in addition to marked physical fatigue, with 10 percent exhibiting severe forms of the response. The most resistant to stress factors are individuals who have experience in working in such conditions and who are confident about their professional preparedness. In emergency situations, enthusiasm alone—that is, a great desire to render assistance to the victims—is not enough. All mobile physician-nurse teams intended for working at the site of the incident and during the evacuation of victims must not only have the skills needed for saving lives and maintaining functions in vitally important organs, but must also be aware of the features associated with the diagnostics of injuries that can occur in accidents and disasters at specific enterprises and sectors.

Efficiently organized assistance in the area of a possible incident and medical triage and evacuation, with support for the functions of vitally important organs and subsequent qualified and specialized care, are achieved via scientific forecasting, development of a fundamental concept, and, on the basis of them, planning of the activity of health care departments in the event that an actual emergency occurs.

#### **Environmental/Climatic and Socioeconomic Features of Belarus**

Belarus is located in a forested, midlatitude zone and has a temperate climate. Within its borders, strong winds (squalls) are possible from any direction, reaching a maximum speed of up to 30 m/sec or higher. In winter, with winds of 15 m/sec or higher, heavy snowfalls that last up to 12 hours are observed. Hurricanes occur as a result of a dramatic imbalance of the atmospheric equilibrium, which occurs during unusual air-circulation conditions. The hurricanes disrupt and damage electric power lines, communications, buildings, and structures.

In the dry season, fires can break out in forested areas, on peat bogs, and in population centers. Forest fires are fostered by adverse weather conditions: high air temperatures, heatup of the soil, and long spells with no rain, which leads to drought and creates the conditions for the self-combustion of peat; strong winds spread the fire

rapidly. Winds from the southwest, the northeast, and the north predominate in the fall and winter; westerly and southerly winds predominate in the summer.

In the spring and fall, with freshets, ice jams, and large amounts of precipitation, water levels can rise a great deal in the Neman, Zapadnyy Bug, Berezina, Pripyat, Zapadnaya Dvina, Dnepr, and Sozh rivers.

Belarus is a republic with developed industry and agriculture. The republic has large amounts of available power and a large amount of automobile, air, and river traffic, as well as pipelines.

**Potentially dangerous facilities of the national economy.** Belarus has no facilities that present a radiation hazard. There is a nuclear reactor 7.5 km to the southeast of the outskirts of Minsk.

Set up around the AES are the following zones: a health-protection zone (3 km), a zone of possible dangerous contamination (30 km), and an observation zone (50 km). Outside the borders of the republic are several active AESs. The Ignalina AES is located 8 km from the Belarus border on the southern shore of Lake Drukshnay. The AES operates two units, each with an RBMK-1500 nuclear reactor, each of which has a nominal power capacity of 1500 MW.

With adverse weather conditions, characterized by a stable atmosphere with a moderate inversion and a wind speed of 2 m/sec, the following contamination zones would result if a 1500 MW reactor were to be destroyed: a dangerous contamination zone (30 rem at the outer boundary: length 145 km, width 6.4 km, area 740 sq km) and an extremely dangerous contamination zone (250 rem at the outer boundary: length 87 km, width 5.8 km, area 400 sq km).

The 30-km zone includes 912 sq km of the Braslavskiy Rayon, with a population of 19,000 people. The 50-km zone covers an area that also includes Miorskiy, Postavskiy, and Sharkovshchinskiy rayons (2,415 sq km, with a population of 39,400 people). Some 65 km from the republic is the Smolensk AES (in the settlement of Desnogorsk, RSFSR). A 70-km zone around it includes some of the Klimovichskiy Rayon of Mogilev Oblast. The Rovno AES (in the settlement of Kuznetsovsk, UkrSSR) is 67 km from the southern border of the republic, and the Chernobyl AES (in the city of Pripyat, UkrSSR) is 8 km from the border. Within a 70-km radius of the former are parts of the Stolinskiy and Pinskiy rayons of Bretsk Oblast. The 30-km zone around Chernobyl AES includes the Braginskiy, Narovlyanskiy, and Khoynikskiy rayons of Gomel Oblast, for a total area of 865 sq km, in which some 1,600 people reside. Within a 50-km radius are all the rayons of Gomel Oblast, covering an area of 2,404 sq km, with 33,770 people.

**Facilities that present an explosion or fire hazard.** Belarus has 243 national-economy facilities that handle fuel

reserves, petroleum semifinished products, and inflammable and combustible liquids and are classified as facilities that present an explosion/combustion or fire hazard.

The facilities that present an explosion/combustion hazard include 18 gas industry enterprises, six thermal energy enterprises that use compressed gas and fuel oil, and four facilities that house dangerously explosive or inflammable substances (Lakraska Production Association, in the city of Lida; power metallurgy plant, in Molodechno; central Gosnab base, in Vitebsk; and paint and varnish plant, in Minsk).

Among the facilities that present a fire hazard, the following must be named: 53 petroleum facilities and storage facilities that house fuel and lubricant materials; 24 enterprises involved in the extraction and refining of peat; 24 facilities of the timber-processing and paper-and-pulp industry; 46 flax-processing plants; 45 enterprises of the grain-products industry; and 23 facilities housing inflammable substances and materials.

**Rail transport.** All the lines of the Belorussian Railroad carry dangerous cargoes that fill 400-1500 cars a month. The lines with the highest volume of car traffic are as follows: Minsk-Brest, Minsk-Molodechno, Gomel-Kalinkovich-Luninets, Vitebsk-Orsha-Mozyr, and Vitebsk-Novopolotsk. Trains that carry dangerous cargoes have stops for the performance of engineering operations at the major railroad stations of the cities and railroad junctions of Baranovich, Gomel, Kalinkovich, Orsha, Zhlobin, Minsk, Mogilev, and Brest. As many as 800 cars per month are loaded at each of the following stations: Novopolotsk, Babarov, Rechitsa, and Auls. Hydrogen cyanide is unloaded at Brest; carbon disulfide, at Mogilev and Svetlogorsk; chlorine, at Svisloch; ammonia, at Auls, Svetlogorsk, Babarov, and Novopolotsk. The dangerous cargoes are delivered from the unloading stations to a number of users by motor vehicle.

**Other facilities that would present a danger to the environment if there were a failure, an accident, or a natural disaster.**

Among the natural disasters that present a danger to the environment are freshets and high water in rivers. The strongest and most frequent freshets are observed on the Pripyat River and its tributaries. As a rule, when they overflow, as many as 50 population centers in Brest Oblast (Stolinskiy, Pinskiy, and Luninetskiy rayons) are flooded, as are as many as 80 population centers in Gomel Oblast (Zhitkovichskiy, Petrikovskiy, Mozyrskiy, Kalinkovichskiy, Narovlyanskiy, and Khoynikskiy rayons). Freshets and flooding take place on the rivers Zapadnyy Bug (Brest Oblast), Zapadnaya Dvina (Vitebsk Oblast), and Neman (Grodno Oblast).

Dams are also dangerous facilities if they break. In Belarus, 15 man made reservoirs holding from 2 million cu m of water to 260 million cu m of water have been created on small rivers and irrigation systems. The

largest reservoirs are the Vileyka Reservoir (Minsk Oblast) and the Zaslavl Reservoir (5 km northwest of Minsk). The Vileyka Reservoir holds 260 million cu m of water. If the earthen floor of the dam were to be breached, 188 sq km would be flooded, an area that contains 28 population centers and the outskirts of the city of Vileyka, with a population of 6,160. The Zaslavl Reservoir holds 108.5 million cu m of water. An area of 39 sq km could be flooded by it, endangering 4,800 people in five population centers and part of the city of Minsk along the Svisloch River floodplain. There are 12 bridges in that area, and they could be damaged or totally destroyed. The other dams, if they were to be breached, would not have any catastrophic consequences, but would require a number of measures to be taken to restore the dams and evacuate the people and farm animals.

**Snow accumulations on railroad tracks.** Observations indicate that heavy snowfalls and storms close down freight and passenger traffic on the following lines: Orsha-Minsk-Brest, Gomel-Minsk-Vilnyus, Mozyr-Vitebsk, Brest-Gomel, and Vitebsk-Verkhnedvinsk.

**Forest fires and peat-bog fires.** Some 35 percent (8.2 million hectares) of the republic is forested. More than half of all the forests (65 percent) represent class I or class II natural fire hazards. Every year, fires break out on peat-bog deposits, which cover an area of 40,000 sq km. In 61 administrative rayons of the republic, in which one-third of the forests and peat-bog deposits are located, an average of as many as 2,300 fires a year break out, often enveloping large areas (in Gomel, Brest, and Minsk oblasts). The annual material losses from forest fires and peat-bog fires amount to 200,000-800,000 rubles. More often than not, the fires occur in the southern rayons of the Brest, Gomel, and Minsk oblasts. The number of forest fires and peat-bog fires increases between the second half of May and October. In certain especially dry years, the number of fires goes up to as many as 4,000-5,000.

Analysis of the environmental/climatic and socioeconomic features of the republic makes it possible to predict the probability of the occurrence of emergencies with a reliability sufficient for producing fundamental data and baseline parameters and to plan the priority measures to be taken to handle them.

Analysis and prediction can be demonstrated with the following sketchy example. In the course of a study of the features of N-Rayon, it was established that the most probable site of an emergency was the chemical combine. It was located in a small area with a population of 80,000. The combine produced mineral fertilizers. The principal raw materials used were compounds based on phosphoric, sulfuric acids, and ammonia. The possible nature of injuries that people could suffer included chemical burns and inhalation poisoning. The probable number of casualties was 10,000 people. The rayon has the capability of earmarking the medical personnel and equipment needed for handling the primary tasks that

would need to be done in the event of an emergency at the combine. And the same can be done for all the chemically dangerous, potentially explosive and inflammable, and railroad facilities of the rayon and oblast. That is, a logical model can be created for each potential situation.

Producing a sound prediction of the probable occurrence of an emergency makes it possible to come up with a completely different concept for the organization of measures for handling any disaster. Underlying that concept must be early planning of operations and special, systematic training of all the components of health care departments and all the personnel of rescue units to handle an accident or natural disaster.

Consequently, in the context of that concept, the process of planning and training health care departments (of the rayon and oblast) for handling any possible emergency situation looks like this:

1. Analysis of the environmental/climatic and socioeconomic features of the rayon and identification of risk factors.
2. Use of a logical model, with a computer if necessary, to predict the nature and scale of the effects of an accident.
3. Planning of the activity of health care departments for a preparatory period and for the period in which an emergency is handled.
4. Training administrative departments, medical units, and the personnel of rescue teams in the handling of an emergency.
5. Buildup and storage of the necessary reserves of materials.

The plan of action for rayon health care departments based on a logical model is a component part of the overall coordination plan of the republic (or oblast). An important condition for its effectiveness is that the main points of the plan be coordinated with involved services and with the departments of the medical services of military units and civil defense. The plan must cover a preparatory period and the period associated with the direct involvement in handling the emergency. The chief aims of the preparatory period are as follows: organize the interaction with the involved services; permanent refinement of the plan of action for the emergency situation; training of medical personnel and rescue units to render assistance in the target conditions; preparation of administrative departments and organizing medical units; and building up and storing material reserves.

The plan for the participation of health care departments in handling accidents, natural disasters, or other emergencies must specify the following: the main tasks to be performed in the emergency situation; a brief description of the especially dangerous facilities; the largest shift in terms of number of workers and the size of the population living in the zone of possible affliction;

possible number of casualties at the facilities and in the adjacent area; the makeup of the personnel and equipment involved in handling the emergency; the organization of the medical care rendered to victims and the medical evacuation of the victims; the arrangements for the availability of medical goods and supplies; and supervision, interaction, and communications.

The plan must include the necessary techniques for calculating casualties and compiling maps of the rayons (or the oblast) showing the location of facilities, possible zones of affliction, and evacuation routes.

The manpower and equipment for handling the most important tasks right after the occurrence of the emergency must be planned to consist of units in permanent readiness, and additional manpower and equipment must come from other medical facilities as the scale of the emergency grows.

The procedures for preparing personnel for handling an emergency situation include a number of well-known methods: practical training in the rendering of medical care with hypothetical victims; medical teams going out along probable routes to the facilities, with their deployment and readiness for work; refinement of the rendering of assistance on the site and during evacuation to treatment facilities; tactical-line studies involving the physician team and the medical unit; solution of situational problems (practical games); training of the rayon health care departments, with refinement of the entire complex of tasks specified in the plan.

The stocks of medical supplies matching the predicted scale and nature of the emergency should be put aside in amounts that will meet the most important needs and should take into account the features of the probable pathology. The supplies should be kept at medical facilities and at medical depots intended for providing supplies in special periods.

The means of improving the organization of medical care for the population in emergency situations reside in methodology. Along with the work under way in the republic in the creation of a system for rapid response to emergency situations, practical realization of this methodology is absolutely necessary: planning and specific, early preparation of republic (and oblast and rayon) health care departments so as to effect a high level of readiness for performing whatever tasks are needed in any circumstances.

In accordance with recommendations of the Civil Defense Headquarters of the republic, special training of health units at facilities of the national economy is being performed by medical workers in a 24-hour program. In addition to the preparation of the health brigades (or components) in the program, health brigade personnel are being trained on the job in study groups in the program "Preparation of Office Workers, Production Workers, and Kolkhoz Workers in Civil Defense," with exemption from classes in which topics in medical preparation are being taught.



A 35-hour course is conducted annually with physicians and mid-level personnel in a program of mandatory special training developed by the republic health ministry.

We feel that the material presented here will help republic health care officials plan and effect measures aimed at ensuring readiness in the rendering of medical care to the population in emergency situations.

### Drug Abuse in Azerbaijan

927C0484A Moscow VOPROSY NARKOLOGII  
in Russian No 1, Jan-Mar 92 (manuscript received  
17 Nov 89) pp 87-88

[Article by E. M. Rzazade, A. K. Abdullayev, R. Sh. Ibragimov, Physiology Institute imeni I. I. Karayev, Azerbaijan Academy of Sciences, Addictology Clinic, Baku; UDC 616.89-008.441.33-036.22(479.24)]

[Text] There is a long history of drug use in Azerbaijan, which can be attributed to a number of cultural, historical, geographical, and economic factors. However, the epidemic situation in Azerbaijan has recently become more acute with the advent of problems in obtaining employment, social upheavals, and the migration of large masses of people.

In mid-1989 there were 1,024 persons on the clinic records for all of Azerbaijan. However, anonymous surveying of different groups of the public suggests that the actual number of victims is 10-12 times greater. Azerbaijan occupies an intermediate place among the other regions of the country with respect to the number of recorded drug addicts per 100,000 persons. However, comparing the number of drug addicts in different age groups revealed that the situation in Azerbaijan is one of the worst. The practice that has developed among some of the people in Azerbaijan of obtaining treatment in central medical establishments of the country, which increases the outflow of potential patients, makes it more difficult to identify and account for them.

Over the past two years we have bitterly observed the disastrous effect of social stress on the epidemiological situation with respect to drug use in Azerbaijan. The number of drug addicts on clinic records has increased by 70.6 percent against a background of increases in neuroses and suicide. In addition, the increase in the number of drug addicts in the cities is much greater than in rural areas ( $p < 0.001$ ), which demonstrates a distinct relationship between the level of care given by medical establishments and the detection of addicts. The drug addicts are becoming younger and the number of those involved with drugs that become addicts is increasing. An average of 74 percent of drug addicts are under 30 years of age. Problems of the rapid diagnosis and identification of risk groups remain urgent in Azerbaijan.

In order to perform mass public health examinations at the Azerbaijan Addictology Clinic, it has been proposed that a mobile laboratory with two automated work sites

for a physician and psychologist be established and equipped with an electroencephalograph, electrocardiograph, PFK-1, magnetograph, and computer-controlled indicator, as well as an automated control system. The matter of the mass health examinations with the participation of Ministry of Internal Affairs agencies will be decided after the details of the methods of mass public health examinations have been worked out.

For now we can discuss the considerable changes in the structure of drug use. The proportion of hashish use that has traditionally dominated among drug addicts in Azerbaijan is decreasing mainly due to the increase in number of opiate addicts using non-traditional types of narcotics such as koknar [an opium derivative], "khimka" [habit-forming chemical], etc. The average proportion of hashish use in Azerbaijan is 56 percent. In rural areas it is 73.8 percent, and in small cities, including suburbs of Baku, it is 60.2 percent. However, in central Baku it is less than 44 percent. The diversity of methods for administering drugs is growing with the spread in the use of non-traditional narcotics. As a result of measures for stopping morphine use, koknar was used in 89.6 percent of all cases of intravenous narcotic use recorded in 1989.

The increase in drug use among women has not yet been recorded. Women comprise less than 5 percent of all addicts on record. However, even here we are seeing an unfavorable trend: the expanding range of narcotics used and methods of their use, use among younger people, and social degradation of drug use. Suicidal behavior was found in 47 percent of female drug addicts examined. Surveys among older schoolchildren revealed that they know more than their predecessors about narcotics and the respective slang. An anonymous survey revealed that 18 percent of urban schoolchildren could name the narcotics found in pharmaceuticals used to treat Parkinson's, and 9 percent could name volatile toxicomaniac substances. As a whole, comparison of the survey results with data on the recorded toxicomania morbidity rate indicate the unsatisfactory situation for detection of victims. Twenty percent of toxicomanics on record are teenagers. Toxicomanics are more likely (36 percent) to have a genetic history of alcoholism or mental disease.

In recent years we have seen an increase in the number of drug addicts with a history of alcohol abuse. Thirteen percent of anonymously surveyed alcoholism patients being treated at the Azerbaijan Addictology Clinic indicated "casual" use of narcotics, mainly hashish. More than 80 percent of those with previous convictions reported occasional use of narcotics. The trend continues in Azerbaijan toward an increase in previous convictions among drug addicts (36 percent of those examined), 32 percent of drug addicts were put on record based on data from criminal affairs, 20 percent were put on record based on police reports. There is a high positive connection between drug use and crime ( $p < 0.01$ ) in virtually all rayons. The rise in the number of crimes is accompanied by a rise in drug use. There was a 16.6 percent increase



in the number of persons arrested for growing narcotic-containing plants from 1988 to 1989. For this same period there was a 15.9 percent increase in the number of persons committing crimes while under the influence of narcotics.

With the increasing power of religion, it would be interesting to analyze the controversial idea that Islamic traditions, which prohibit the use of alcohol, at the same time seem to stimulate the spread of narcotics. During the course of examination, the utilization of vocabulary with religious expressions was established in 14 percent of hashish users. However, this was generally associated with the influence of the immediate surroundings of the victims. In addition, there was a complete lack of a critical attitude of those examined toward alcohol. At the same time, the surveyed believers declared that any form of drunkenness was incompatible with religious convictions. Typically, there are no national barriers or limits to those who abuse narcotics; rather, the national make-up of the addicts corresponds to general population data for all of Azerbaijan.

We have recently seen some shifts in the reasons for beginning narcotic substance abuse. In comparison with past years, we are seeing somewhat more of imitation and inclination. Other reasons include curiosity (50 percent), self-treatment (18 percent), and doctor's prescription (3 percent). More than 3 percent of victims became addicted to narcotics during military service.

Numerous problems with the treatment and rehabilitation of drug addicts face us. At present the goal of 63 percent of all drug addicts admitted for treatment is to reduce their tolerance to the narcotics. There is a high incidence of relapses within the first year of treatment. Over the past few years 48 percent of drug addicts were taken off the record when they were sentenced to prison. The low percentage of requests for anonymous care is typical. Analysis of anonymous requests on a special telephone line showed that most calls for help were from repeat drug addicts or drug addicts who began at a young age, but who lack the direction for treatment. Anonymous care for drug addicts needs to be improved. It is currently only of a medical nature. Anti-narcotic advertising has been unsatisfactory due to the poor coordination of measures, lack of professionalism, and shortage of respective scientific advances. Among those surveyed, the overwhelming number of students and approximately half of workers believe that anti-narcotic advertising is helpful. However 60 percent of teachers believe it is ineffective, and 15 percent believe it is harmful, since in their opinion it evokes an unhealthy interest in narcotics in the students and gives them unneeded information. In view of the clear need for conducting prophylactic work among the public, especially among risk groups, we need to improve the currently extremely ineffective popularization and propaganda measures.

We need to study and summarize the experience of work by informal organizations among youth groups that abuse various toxicomanic substances. Work by the

informal group "Tovba" (repentance, confession), which is based on ancient traditions of spiritual and physical purification, has stimulated a great deal of interest. The popularity of similar organizations may be due to the breadth and complexity of measures used, from the effect on religious feelings to intense physical exercise, and even forgotten folk medicine remedies, such as the eastern bath.

The complicated situation arising in Azerbaijan in connection with the growth in drug addiction revealed the problems in the system of anti-narcotic measures and the lack of technical support, weakness in forecasting, and ineffectiveness of prophylactic measures, especially among risk groups. We need to develop a more dynamic and effective, integral program that covers the various aspects of the problem.

### Decentralization of Pharmaceuticals Industry

927C0485A Moscow FARMATSIYA in Russian  
No 1, Jan-Feb 92 pp 1-3

[Editorial]

[Text] The journal FARMATSIYA now enters the year 1992. This year is of particular importance as a year in which radical economic reforms are being implemented and a transition is being made to market economy management within a single economic domain and as a year in which the Community of Sovereign States has been formed.

Pharmaceutical scientific research and applied institutions are directly participating in the process of perestroika and are pursuing their own and often non-traditional methods of resolving new complex problems related to the provision of drug products for the population and therapeutic-prophylactic institutions under market economy conditions.

Profound changes are taking place within various levels of pharmacy services as well as in their relationships to industry and the other health sectors. The organization of scientific research in pharmacy, its funding and practical implementation are being structured anew. New approaches are being sought for the training of specialists with higher and middle-level pharmaceutical education, for improvements in the academic process and for better training of pharmacy supervisors and dispensing pharmacists and for raising their skill levels.

The sovereign states have concluded economic agreements whereby practically all questions related to the activity of health authorities and institutions, pharmacy services, and the pharmaceutical industry will be turned over to the competency of the sovereign states. Only activities related to metrology and standards would be regulated by coordinated efforts. The inclusion of a system of governmental quality control of drugs and medical equipment and standardized specifications for these agents and products would be desirable. The governments of the sovereign states have affirmed the need

to coordinate policy development in the area of sanitation-prophylaxis and anti-epidemic measures.

The implementation of these measures by the authorities and administration of the constituent states is slated to be accomplished by coordination and special agreements. In light of these decisions there will be a larger role and responsibility given to a unified inter-republic publication for pharmaceutical personnel in order to consolidate the efforts undertaken to carry out the overall tasks of providing medication to in- and out-patients.

Under these extremely complex conditions in which there has been a breakdown of the old traditional structures of command-administrative sector administration and where we are shifting to contractual relationships on new legal and economic basis, we envisage the goal of our journal as an operative elucidation of all new developments in the practice of pharmacy services so that all emergent problems can be resolved in a competent and business-like manner through maximally methodical and organizational approaches as well as legal and economic substantiation.

The system of medical equipment and drug supply is undergoing a radical restructuring. The transition to direct contact between consumers and manufacturers of medical products without the participation of middlemen at the union, and subsequently at the republic level, requires a new formulation of these operations in the FARMATSIYA primary link associations.

The management system of the pharmaceutical industry is undergoing change at the same time. The USSR Ministry of the Medical Industry has been eliminated. Its subordinate enterprises have formed the "Farmindustriya" state corporation and the "Biopreperat" and "Immunopreperat" concerns. Several of their plants and territorial associations have decided to become completely independent. Republic associations of pharmaceutical enterprises are being formed.

These peculiarities of the transition period require new approaches to the organizational operations of the sectors of pharmacy services and pharmaceutical scientific research.

Under these conditions it is very important to preserve the integrity of our pharmaceutical research sector. Progress in our domestic pharmacy operations cannot be made without the development of scientific research, particularly fundamental research. A broad exchange of scientific research is particularly essential at the present time. An elucidation of this restructuring will also be among the principal tasks of our journal.

Special attention will be given to the publication of materials on improving the manufacturing processes of medicinal agents. This will help fill market needs by expanding the manufacture of drugs both at plants and factories as well as at small enterprises.

The publication of articles is being planned on subjects dealing with the theory and practice of pharmaceutical analysis. We are planning to acquaint the reader with modern methods for research on homeopathic drugs and plant preparations. Publications on standardized analytical procedures and means of higher drug quality control will be continued.

The journal will publish literature reviews on resolving problems in pharmaceutical science and practice. This will make materials available and accessible that are oftentimes known to individual specialists only.

We are also planning to continue the publication of materials dealing with personnel training with the purpose of raising the pedagogical skills of instructors and improving the quality of their training.

In 1992 the journal FARMATSIYA is planning the continuous publication of articles on pharmaceutical information, new organizational-methodical forms of pharmacy service operations, and on improvements of information technology.

A number of articles will be concerned with the operations of pharmaceutical information departments and subdivisions at various levels of organization under our new economic conditions.

The "New Medicinal Agents" column will continue to acquaint health specialists with new effective preparations manufactured both here and abroad.

The editorial board believes that the structure of the journal should be retained but that greater emphasis should be given to materials dealing with scientific and practical operational aspects of pharmacy institutions under our new conditions.

In order to broaden the knowledge of pharmacist supervisors and dispensing pharmacists we are planning to continue and develop the "Consultation" and "Medicinal Plants", etc. sections.

Of course, the above-mentioned areas do not represent an exhaustive list of problems that will be covered in our journal.

The effectiveness of the information contained in the journal is determined not only by the plans of the editorial board and editorial council, but by its contents and quality of the articles sent to the journal. The journal FARMATSIYA in the person of the editorial board members, science reviewers, and members of the editorial council have accorded assistance and will render assistance to scientific research and applied workers, and particularly to young associates in the selection of topics for their articles and assist them in their preparation of the articles. We hope to expand this tradition which will raise the quality of the material being printed and constitute a school for young workers.

The timely importance and quality of the material published constitute the most important task of the journal.

However, the rapid publication of articles received is also important. Unfortunately, for technical reasons several months are required before an article that has undergone a review and scientific editing can be published. In order to accelerate publication there must be a significant improvement in the quality of the articles received by the editors as well as a better observation of the rules governing their format. These rules are regularly published in the journal. The editorial board is presently compelled to delay the publication of many articles that require clarification of text and illegibly written symbols, corrections of captions for diagrams, bibliographic data for inscribing conclusions, etc.

The task of our journal is to call the attention of our readers and the considerable collective of authors to the improvements in the journal's operation. The editorial board and the SOYUZFARMATSIYA association have conducted a poll of pharmacy services personnel for the purpose of eliciting their views as to what they would like to see in our journal. We have received many suggestions and desiderata (and very interesting ones). Thanks to all who have already responded and to those who plan to do so. Your suggestions will not only be taken into consideration, but will be published if space permits.

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# **Pharmacy Operations in Moldova Under New Economic Conditions (First Results and Prospects)**

927C0485B Moscow FARMATSIYA in Russian Vol 41  
No 1, Jan-Feb 92 (manuscript received 13 Jul 91) pp 3-6

[Article by I.S. Rybak, V.I. Prokopishin, Ch.Ya. Krimerman, and V.N. Safta, Rayon Production Association FARMATSIYA, Ministry of Health of the Republic of

Moldova, Kishinev Medical Institute im. N.A. Testemitsan; UDC 615.1(478.9):658.155]

[Text] The quest for new management methods and their implementation have taken on special importance for pharmacy institutions and associations in the light of the transition to a market economy. In that connection, beginning with January 1989, the pharmacy network of the Republic of Moldova, along with an administrative reorganization, has been transferred to a total cost-accounting system and self-financing that is based on a standardized distribution of income representing the difference between gross imposition of taxes and total costs.

The entire concept of total cost accounting and self-financing holds that the income (cost accounting income) remaining at the disposal of an association after obligatory deductions based on an established standard, should be distributed by a standard into a fund for industrial and social development. The balance would go into a consolidated wage fund. The industrial and social fund would be used for social development (housing construction, social needs of the collective) and for production development (construction of pharmacies, pharmacy equipment, increases in the level of internal working capital, partial recovery of expenses for personnel training, and other expenditure items). A unified labor cost fund includes the payment of wages and material incentives. The actual deductions from income that go into the budget, wages, production and social development, as well as into a centralized fund for production and social development and reserves will be realized as an incremental total at the start of the year. Associations operating at a low profit and associations whose incomes do not cover planned expenditures and those which receive subsidies from the centralized fund, do not correlate their expenditures and other deductions with the budget.

## **Principal Activity Indices of the Republic Production Association "Pharmacist" of the Moldovan Republic Ministry of Health for the Period 1988-1990**

| Index   | 1988   | 1989  | 1990   | 1990 as % of 1988 |
|---|--------|-------|--------|-------------------|
| Total sales of drugs and medical supplies, millions of rubles                   | 70.7   | 78.5  | 94.5   | 133.7             |
| Average consumption of drugs per inhabitant in one year, rubles                 | 13.95  | 15.32 | 18.76  | 134.5             |
| Average monthly wage of one worker, rubles                                      | 139.09 | 154.8 | 220.98 | 158.9             |
| Average annual material incentive fund per worker, rubles                       | 313    | 428   | 630    | 201.3             |
| Average annual social-cultural and housing construction fund per worker, rubles | 47     | 64    | 108    | 229.8             |

The transition to the republic's pharmacy network to the new management conditions at stable economic fixed standards provides for the complete economic independence of the labor collectives in the formation and utilization of funds.

The experience accumulated by the rayon and city "Pharmacist" associations and by the system as a whole has convincingly demonstrated that the operations under the new economic conditions have improved the provision of medicinal preparations and medical supplies for the public (see Table).

The volume of drug and medical supplies sales in 1990 was 23.8 million rubles greater than the 1988 volume. Those sales to the public increased by 34.5 percent. Approximately 1.3 million rubles were allotted for the development of the pharmacy network and the acquisition of equipment.

The new management conditions have made it possible to allot a significant amount of funds for the material incentive and the collective's social needs. As a result of a 9.1 percent increase in income per worker derived from sales, and the increase in wages, the average monthly wage fund per worker was 58.9 percent greater than 1988, and the funds allotted for social needs grew by 2.3 times.

At the same time a social security fund was formed for pharmacy employees in the rayon (city) "Pharmacist" associations which is being utilized as a supplement to the pensions of unemployed retirees. The amount of deductions placed into this fund for 1990 totaled 68,000 rubles. This fund is growing and being expended strictly in accordance with its designated purpose. In addition, the social development funds are being made available to render assistance to workers in both cooperative and individual housing construction.

Thus, the introduction of the new management mechanism is of considerable interest to each worker in the pharmacy services sector with respect to the end result of his own labor.

However, whereas the "Pharmacist" republic production association of the Moldy Ministry of Health is one of the most profitable republic and oblast "Pharmacist" associations (the profit level for 1990 was 7.64 percent), after two years of operating under the new economic conditions it is losing sight of the carefully established principles of complete cost accounting and self-financing because of the inadequate system of setting prices for medicinals and medical supplies.

At the present time the entire pharmacy service is subsidized and compensation for losses is made quarterly by the republic's Ministry of Finance in accordance with accounting data.

Funds are allotted monthly at 1/12 of the annual loss for the following items:

- recovery of the difference in prices;

- outlays, including wage increases for pharmacy employees and compensation at a rate of 65 rubles per month;

- consumption and accumulation funds as stipulated within the amount in the financial plan.

In connection with the economic situation thus created as well as the forthcoming activity of the pharmaceutical service under the conditions of a sovereign republic, the introduction of unified effective system of price-setting or drugs is one that demands immediate attention.

We believe that the results of the pharmacy institutions' primary activity should not be directly dependent upon price-setting. Therefore, we suggest that the retail prices for medication and medical supplies should represent no less than a 30 percent markup of the wholesale cost.

The manufacture of drugs derived from local raw materials takes on vital importance under the new economic conditions. The organization of a pharmaceutical-industrial complex is being planned in order to resolve that problem. A republic scientific-production center has already been formed and its principal task is to conduct scientific research on producing competitive preparations principally derived from local raw materials.

Subsequent relations with suppliers should be built upon economic trade agreements with other countries, republics, and oblasts and should also be based on direct agreements with industrial enterprises, scientific-production complexes, and foreign firms.

However, during the transition period and until such time as the market for all the important drugs has been satisfied, we believe that the centralized distribution of funds for preparations manufactured in limited quantities should be kept on a contractual basis.

Special attention will be given to the system of training, advanced training, and certification of pharmaceutical personnel. The training of personnel is to be accomplished in stages: at the lyceum, college, and university where appropriate titles will be awarded along with duty assignments. The proposed term of training at the university is six years. In addition to the traditional disciplines, plans are being made to introduce the following new courses: pharmaceutical ecology, psychology and medical ethics, the principles of pharmacy law, the principles of computerization in pharmacy, management, etc. After the successful defense of the diploma dissertation, the graduate will be awarded a temporary diploma allowing him to work as a qualified intern-pharmacist during his first year of employment. In the second year he will given the position of pharmacist-trainee. After two years the qualified pharmacists are certified and are awarded a permanent diploma and general practitioner's certificate. Some graduates may enroll into a two-year clinical pharmacy program. At the same time there is a need to reexamine the list of special fields, as well as qualifications and the corresponding pharmaceutical positions.

Subsequent restructuring in the system of drug supply provides for a reorganization of pharmaceutical services administration with due regard given to changes in the territorial-administrative division of the republic and the Law on Local Self-Government; a broad automation of manufacturing processes based on computerization; intensification of scientific research, etc.

The realization of the indicated directions as well as other trends in the development of pharmacy in the Moldy Republic will be possible under conditions of an effective development of all sectors of the economy, the participation of the republic in the common-union and international markets as well as in the stabilization and improvement of economic and social processes.

### Conclusions

1. The experience of two years gained by the pharmacy network of the Republic of Moldova under new economic conditions has been summarized. The considerable effectiveness of the pharmaceutical service's operations during the transition to full cost accounting and self-financing has been demonstrated.

2. Several ways of perfecting the new economic mechanism and the training of personnel have been proposed that are being tested in the pharmaceutical system of the Moldova Republic.

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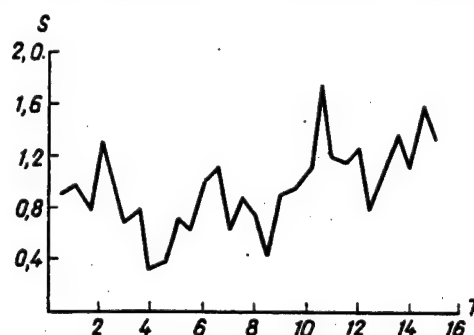
### Improvement in Merchandise Storage at Pharmacy Warehouses

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Vol 41 No 1 Jan-Feb 92 (manuscript received  
03 Jan 91) pp 51-54

[Article by I.B. Yevgrashin, N.V. Nichkova, Yu.L. Danilov, and V.G. Nesterenko, Perm Pharmaceutical Institute, Chelyabinsk Oblast "Farmatsiya" Production Association; UDC 614.27+615.12]

[Text] The material-technical base of pharmacy warehouses have been recently undergoing intensive renovation and expansion. In that connection, pharmacy personnel are faced with questions concerned with the operation of warehouses under the altered conditions. One of the problems concerns the placement of commodity stock at storage departments. The resolution of this problem is tied to the task of creating departments with an optimal operational capacity. This operational capacity can be described by two factors—the annual

commodity turnover and the quantity of product items stored in at a commodity department. The workload for personnel can be distributed evenly in the course of organizing departments with the necessary operational capacity. At the same time the operational costs of the warehouse can be reduced by economizing on the wage fund. We propose a computer-generated method for selecting the optimal capacity of departments. The optimal criterion employed by this computer program constitutes the maximum uniform distribution of workload per worker of various specialization categories. This method is based on the fact that the staff workload norms do not represent multiples of each other. This means that for one category of workers a department may exhibit an optimal capacity, but for another category there might be an "overload", and yet in another the capacity might represent an "underload." In that connection we calculate the cost of the cumulative deviation from an optimal production workload of the department's personnel. The volume of departmental operations at an annual interval of 0.5 million rubles after which the staff force and cumulative deviation are calculated. The staff force is calculated in accordance with the staff standards cited in the literature [3,4,6]. The resultant relationship between the change in the cumulative deviation and the department's capacity represents our model for the efficient utilization of a department's wage fund. The model has several extremal points. The maxima indicate the capacity of departments whose organization is economically undesirable.



Model of actually established wage fund deviations from the calculated fund upon altered departmental work volume (model is for a warehouse which supplies over 300 pharmacies).

X-axis represents departmental commodity turnover (T); Y-axis represents deviation (S), thousands of rubles, annually.



Table 1. Optimal Capacities for Pharmacy Warehouse Storage Departments

| Number of institutions involved in warehouse supply | Capacity of departments, millions of rubles in wholesale prices |                           |
|---|---|---------------------------|
|   | Optimal   | Non-optimal               |
| Under 60  | 1 5.5   | 0.5 3 4                   |
| 61-120  | 1 2.5 3.5 7   | 0.5 1.5 4 5 8             |
| 121-180   | 1 3.5 4.5 8.5 9.5 10.5 11.5 12.5                                | 0.5 1.5 6.5 10 11 14      |
| 181-240   | 1 2 6 9.5 10.5 14   | 0.5 4 8 9 10 11 12        |
| 241-300   | 4 7 10.5 11.5   | 0.5 1.5 5-6 9 10-11 13-14 |
| 301-360   | 1 4 8.5 12.5  | 1 2 6.5 10.5 12 14.5      |

Note: The table lists possible commodity turnovers for departments whose organization is desirable or undesirable. By employing the table one can select departments of the required capacity for each warehouse.

The minima correspond to the capacities of departments which should be organized. One of the models is given in the diagram as an illustration. Table 1 presents the results for modelling the operational volume of departments for warehouses of variable capacity. For example, the warehouse that supplies 181-240 pharmacies should be provided with departments with an operational volume of 1, 2, 6, 9.5, 10.5 or 14 million rubles annually. The formation of departments with an operational volume of 0.5, 4, 8, 9, 10, 11 or 12 million rubles would not be efficient. By utilizing the results in Table 1 one can select the required number of departments with an optimal capacity for any warehouse, i.e., the multiversity approach built into our method allows the administrative offices of a warehouse broad possibilities for substantiating organizational designs for its warehouse operations. The possibility of taking into account specific warehouse operational conditions is no small factor under conditions of managerial economic independence.

An analysis of warehouse operations shows that each warehouse has its own peculiar commodity storage characteristics that are independent of the warehouse's operational volume (the examined warehouses were non-classified). The warehouse departments have various areas of specialization, i.e., they have many variants and combinations of product items stored in the commodity departments. These peculiarities primarily apply to the departments which store medicinal agents. The examined warehouses had 38 types of specialized operational departments. For example, they included the following departments: antibiotics and vitamins; antibiotics, bacterial preparations, and medicinal plant materials; antibiotics and sulfonamides; medicinal herbs and pharmaceutical products; vitamins and antithesis agents; bacterial preparations and blood substitutes; antibiotics; blood substitutes and medicinal plant materials; bacterial preparations; galenics, etc. As one can see from this example the same category of items at the warehouses is distributed among different storage departments. Therefore, the problem of organizing commodity storage at the warehouses is a vital one. The most elaborated principles of storage are those that are based on the nature of the medicinal form, physico-chemical properties, environmental factors influencing product shelf life, etc. [1, 2, 5]. In the present study we attempted to devise a system of drug

storage with respect to the pharmaco-therapeutic properties of the medicinal agents. The remaining principles of storage organization were also taken into consideration. The approach we propose facilitates the job of adjusting pharmacy requirements, i.e., the specialized work of commodity experts in the marketing departments is done with respect to the storage departments.

The following factors were taken into consideration in regard to the distribution of medicinal agents among the departments: pharmaco-therapeutic action; the number of drug items; the departmental turnover; the distribution of agents by groups in annual requisition-orders, and medicinal storage conditions. We also analyzed the medicinal agents by pharmaco-therapeutic groups. We took as our basis the classification by groups adopted in the annual requisition-orders which introduce uniformity into organization of supply operations. The number of drug list items is highly variable, i.e. ranging from 3 to 312. Most drugs exhibiting the same action were distributed into different groups. For example, analgesics were tabulated into three groups (07 - analgesics, antipyretics and anti-inflammatory agents, and pyrazolone derivatives; 08 and 09 - analgesics, antipyretics and anti-inflammatory agents, salicylic acid derivatives). Antiseptic agents form six groups. Therefore, we combined similarly acting agents into enlarged groups. This took into consideration the number of drug list items, storage conditions, and drug turnover by group. We immediately separated into a separate group agents which must be stored in the department of toxic and narcotic agents (group 05, 06, 19, 45, 73, 84). The following preparations were consolidated into individual groups: bacterial and viral preparations; antiseptics and antimicrobial agents; emetics and expectorants. Vitamins, hormones, and enzymes were included into the group of agents affecting metabolic processes. Antibiotics and sulfonamides were consolidated into the group of agents with antibiotic activity. Agents acting upon the central nervous system (for narcosis, soporifics, and psychotropics) made up yet another group. Agents affecting the sensory nerve endings (afferent innervation) such as analgesics and anesthetics were consolidated into a separate storage group. Cholinergic, adrenergic, dopaminergic and histaminergic agents formed a group of agents that act primarily on the peripheral neuromediator processes.

Characteristics of Variable Distribution of Medicinal Agents by Storage Departments

| No. of variant | No. of departments* | No. of medicinal agent groups in accordance with annual requisition requests | Commodity turnover, millions of rubles** | Number of drug list items |
|----------------|---------------------|--|--|---------------------------|
| 1              | 1                   | 1-4, 10-13   | 2.5                                      | 252                       |
| -              | 2                   | 7-9, 20-26, 33-35  | 6.1                                      | 288                       |
| -              | 3                   | 14-18, 27-32, 51   | 5.7                                      | 319                       |
| -              | 4                   | 59-67  | 3.0                                      | 254                       |
| -              | 5                   | 68-72 74-82, 87, 90  | 1.7                                      | 281                       |
| -              | 6                   | 37-44 46-50  | 8.6                                      | 328                       |
| -              | 7                   | 36, 52-58, 85, 86, 88  | 3.4                                      | 295                       |
| -              | 8                   | 97   | 0.5                                      | 312                       |
| 2              | 1                   | 1-4, 7-13  | 4.8                                      | 317                       |
| -              | 2                   | 14-18, 20-28   | 4.4                                      | 336                       |
| -              | 3                   | 29-36  | 4.9                                      | 208                       |
| -              | 4                   | 37-44, 46-53   | 10.1                                     | 418                       |
| -              | 5                   | 54-58, 76-82, 85-88, 90  | 2.5                                      | 324                       |
| -              | 6                   | 59-72, 75, 75  | 4.3                                      | 414                       |
| -              | 7                   | 97   | 0.5                                      | 312                       |
| 3              | 1                   | 1-4, 7-13  | 4.8                                      | 317                       |
| -              | 2                   | 14-18, 20-26   | 4.6                                      | 307                       |
| -              | 3                   | 27-36  | 5.0                                      | 237                       |
| -              | 4                   | 37-44, 66-67, 97   | 5.4                                      | 499                       |
| -              | 5                   | 46-56, 85-88, 90   | 7.1                                      | 428                       |
| -              | 6                   | 57-65, 68-82   | 4.6                                      | 536                       |
| 4              | 1                   | 1-4, 10-13, 27-32  | 6.6                                      | 417                       |
| -              | 2                   | 7-9, 14-18, 20-26, 33-35, 51   | 7.7                                      | 442                       |
| -              | 3                   | 59-72, 74-82   | 4.6                                      | 509                       |
| -              | 4                   | 46-49, 97  | 3.5                                      | 467                       |
| -              | 5                   | 36-44, 50, 52-58, 85-88, 90  | 9.1                                      | 497                       |

\* The department for toxic and narcotic substance storage as well as the departments for the storage of the remaining drug items are not shown. The previous storage principle applies to that list.

\*\* Illustration for a warehouse with a drug turnover of 50 million rubles.

The multiversity approach was adopted for the distribution of agents by storage departments. This allows the warehouses to select the most suitable variable of storage organization with respect to economy, material base of the warehouse, and organizational structure. The drug turnover of departments was selected with economic effectiveness whose principle was examined previously. Four variants with different numbers of departments have been suggested (Table 2). Each variant has its own advantages and shortcomings. For example, variant No. 4 has the most uniform distribution of drug items stored within its departments, although the drug turnover is not optimal. Variant No. 3 is the closest to an optimal drug turnover, although it has the greatest number of differences in the types of drug items stored in the departments.

The results of our study have been tested in the organization of a new oblast pharmacy warehouse in Chelyabinsk. The storage departments of that warehouse contain medicinal agents grouped by pharmacotherapeutic designation and in accordance with the departments' optimal capacity. An economic analysis has shown that there can be a possible 4-6 percent savings in the wage fund of workers in the operational departments. The effectiveness of the project was evaluated by the time required to recoup the funds expended on the study. The expenses were evaluated by the largest expenditure items, i.e., the wage fund and research travel expenses. The calculations demonstrated that the expenses are recouped within a short period of time, i.e., no longer than seven months. This indicates the highly effective nature of the research project.

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### **Health Care Reform in RSFSR (Brief Version of Concept)**

927C0486A Moscow ZDRAVOOKHRANENIYE  
ROSSIYSKOY FEDERATSII in Russian No 2, Feb 92  
pp 3-7

[Article by A. A. Askalonov, President of RSFSR Supreme Soviet Committee on Health, Welfare, and Physical Education]

[Text] A set of urgent measures for implementing economic reform, which is a concentrated expression of economic approaches and public protection measures, has prompted an acute need for reform in public health protection in the RSFSR.

In the first place it is necessary to move from perceiving health care as a legal-humanitarian category toward an economic one. It is the physical and intellectual health that is the chief capital of society; therefore, concern for maintaining and improving public health cannot and must not be decreased, since growth of the economic potential of the state depends on it. An unhealthy nation cannot prosper economically. Taking into account the fact that public health is a determining factor in the biosocioeconomic maintenance under conditions of government reform, it is necessary to determine the most important directions in health protection and its structural policy.

Economic reform of health care dictates moving from the branch level of development to a national level,

which would make it possible to depart from the residual principle of financing and develop a new model of mixed budget-insurance medicine. The balanced combination of budget, social insurance, and individual sources of financing health care necessitates radical reform in the organization and management of medical care.

The events in our country indicate the need for developing public health protection on a republic level based on the passage of political and socio-economic resolutions. Political resolutions convince us of the need for decentralization, the development of self-managing territorial programs for health protection, and improvement of the state system, along with the use of different forms of ownership.

The socio-economic resolutions are aimed at increasing the purposeful accumulation and use of resources in the field of public health protection, increasing the economic interest of all of society, enterprises, citizens, and medical personnel in health protection, with the reasonable and efficient use of resources. The status of public health and the actual position of health care convince us of the need for extensive and radical changes that equally affect the structural, functional, and financial questions, the training and advanced training of medical personnel, wages, etc.

The task at this level is to create such a system of public health protection that would satisfy the needs of society for health protection and take into account the capabilities of the republic's national economy. Introducing reforms only within the health care system itself will not solve the problems of maintaining and improving public health, since to a considerable degree it is associated with the socio-economic and political situation in society. The majority of factors public health are not managed by the public health system, and the system does not directly or indirectly affect them. The public's quality of life, the condition of the environment, including the air, water, food, and soil quality, work and living conditions, and sense of public danger, stress, and mental stress are the result of socio-economic activity, the economic situation of the country, and the result of management methods.

In connection with this, the first direction of reform is to develop a system of public health care and alter the management of public health protection based on a comprehensive approach which would protect the interests of the government, social, and economic organizations and the public itself. At territorial levels (oblast, municipal, rayon) it would be wise to establish public health and welfare councils that unite representatives from government, occupational self-government of health care workers (associations), society, and the public who are involved in solving problems that concern the internal operation of these establishments. The introduction of economic reward for the interested relationship of management agencies, entrepreneurs, and the public itself is a fundamental component of an actual operating system of public health care.

The guiding principles of the effective function of the health protection system are the legal and economic responsibility of a manufacturer for the production of goods that harm the health of the entire public or individual groups; the economic responsibility of all entities of economic activity for an action that negatively affects the environment and public, the economic interest of the government, establishments, enterprises, organizations, and public agencies in improving health; the actual interest of health care personnel in the results of prophylaxis, diagnosis, treatment, and rehabilitation among different groups of the public.

The second direction of reform is the gradual introduction of medical insurance for citizens in accordance with RSFSR law.

Medical insurance is a form of social protection of the public's interests in the field of health protection. The goal of civilian medical insurance is to guarantee the public that they will have medical care for diseases using accumulated resources, as well as the funds for prophylactic measures.

Medical insurance will be available in both mandatory and voluntary forms.

The law orders the legal regulation of medical care for citizens of the Russian Federation under conditions of the formation of a market economy. The core of the law is the budget-insurance model of financing health care which first of all implements the principle of public solidarity in the field of public medical service.

The law, by keeping the positive sides of the current health care system (free medical care within the framework of mandatory medical insurance, universality, and accessibility), increases the responsibility of the state, enterprises, and citizens in matters of public health protection and equalizes socially unjust differentiation in the rendering of medical services.

The law lays the foundation for the social protection of the public under the new economic conditions. This foundation stipulates abolition of the monopoly of the health care system in the field of public health protection, radical changes in the resource support of health care, including its financing and the economic activity of medical establishments.

The medical establishments become legal, independent economic entities with different forms of ownership. Their activity will be based on negotiations with insurance organizations.

It is stipulated that medical establishments will be financed for a given volume and quality of work actually performed. This will be specified by the conditions of the agreement.

Medical establishments (polyclinics, hospitals, scientific research and medical institutes, persons involved in individual labor activity, individual physicians, and groups of physicians) may only work in the medical

insurance system if they are accredited and licensed. According to law, the medical establishments and health care management agencies cannot found insurance organizations or hold stock in medical insurance organizations. These limitations will strengthen the anti-monopoly policy in the field of public health protection.

Legal responsibility of medical establishments is being introduced for the volume, period, and quality of medical care and for refusing to care for an insured party. The insurance organization acts as an independent expert on meeting the conditions of the agreement, and when the agreement is violated the insurance organization lodges a claim against the therapeutic establishment for moral and physical damages caused the insured party.

The third direction in reform is the scientifically based differentiation of functions by levels of management.

The health care system assumes the existence of the following levels of management: rayon, oblast, and republic. The functional level, which in the end fulfills the planning and coordination role, is the regional level, which determines the interaction of the oblasts and republic.

The main territorial subunit (municipal, rural rayon) should become the primary structure of health care organization and the organization and financing of social care. The authorities at this level bear the full responsibility for providing their territories with the services in the field of primary medical care and the bulk of social care. These tasks can be met only by taking into account the public opinion and with the involvement of local self-governments in close cooperation with competent territorial agencies of occupational self-governments, as well as in cooperation with medical insurance system management agencies. At the rayon level organizational tasks concerning the satisfaction of needs in the field of specialized care, such as outpatient and inpatient, are also carried out. Similar changes will result in a situation where the rayon level will be organized from below by the main territorial subunits that are involved in establishing the conditions for meeting the needs of their residents for health protection.

The needs of health protection should be met at the oblast level for those specialties whose organization at the rayon level would be impossible or unprofitable from the point of view of comparing expense and effect. The oblast (kray) is a rather large territory for which to plan and organize a considerable portion of health protection measures based on a balanced volume of needs issuing from assessment of the health condition and the possibilities for satisfaction from the point of view of the volume of available resources (personnel, infrastructure, network). The organization of the oblast level of health care and selection of its forms should be based on the principle of subjectivity of the subunits at the primary (rayon) level.



The regional level, although not yet formally acknowledged as such, is already playing an extremely significant role in satisfying the needs for narrowly specialized medical care. The basis for this type of work is the clinics and subunits of medical higher educational institutes and departmental scientific research institutes. The recognition of this level will make it possible to eliminate the often ineffective base of narrowly specialized services that is organized at the oblast level.

In this case, in addition to clinic establishments, medical academies, and institutes financed by the republic, the oblasts can conclude agreements that organize and finance narrowly specialized medical care at the regional level (interoblast level). Thus, they will be able to avoid the inefficient use of resources caused by the organization of narrowly specialized care and also improve the quality of training of medical personnel by supporting it at interregional and republic levels.

At the regional level a balance of needs for health protection should be developed by analyzing the epidemiological situation. The medical higher educational institutes and competent scientific research establishments and the centers for meeting these needs should perform this analysis and include an assessment of the possibilities of training specialists for the oblasts to cooperate within the region.

The decentralization of tasks associated with the current management necessitates concentrating attention at the republic level primarily on strategic tasks. In the first place, this concerns the process of developing general prerequisites and basic directions of health protection as an integral component of the integrated social policy of the republic.

Programs for public health protection in the republic should be developed, coordinated, and implemented at the republic level. Republic level agencies should have the resources for implementing the particularly important special programs. Their role is to assist in satisfying the needs of health protection based on the chief demographic, social, and epidemiological problems of the republic, as well as to take measures aimed at reducing disproportion in the functioning of health care and social care in different parts of the republic or with respect to social groups whose health is at special risk. The following problems need to be worked through and solved at the republic level based on analysis, assessment, and forecasting of the status of public health and its needs for medical care: specificity of organization of public health in the republic, forms of coordinating work, adopting the highest standards, the manufacture and purchase of equipment, instruments, medical goods and drugs, personnel training, scientific research, and international connections.

Considering the fact that there are no scientific foundations of health protection under conditions of a market economy, the oblasts need management theories with the use of modern methods of system analysis to construct a

concept and "tree of ideas" of purposeful computerized democratic management of health care at different levels. Basic concepts and socio-economic subjects of health care such as the social sphere under conditions of moving to a market economy need to be formulated; a theoretical model of integrated interdepartmental process of managing health protection needs to be established to determine the strategy, quality, pace, and proportion of development.

A systematic methodology of health care management needs to be proposed in the field of management to include the socio-political, economic, organizational and distribution, and socio-psychological methods of management that will increase responsibility for the end results. Methodical approaches to improving the process of health care management in a territorial respect with consideration of the expanding boundaries of the independence of health care management and medical establishment agencies need to be developed. Methodical approaches to solving the components of the management process need to be established, especially the development of a sociological management method, methods of economically oriented activity, and socio-psychological methods of involving the public in health protection.

The fourth direction in health care reform stipulates the establishment of conditions for protecting health in accordance with 38 points outlined by the WHO, including reducing the differences in the level and quality of medical care to different groups of the public in different territories, reducing disability, reducing morbidity, especially with respect to diseases of the circulatory system, cancer, reducing the frequency of accidents, and indexes of infant and maternal mortality, and increasing the average life span. In order to improve the quality of life and health, the state in the person of the Council of People's Deputies should at all levels support the development and implementation of a policy aimed at improving health and a system of social support and information dissemination with respect to how to improve health and the material resources for it. The Council of People's Deputies should also implement a system of penalties for establishments, organizations, and citizens that damage individual or public health. Legislation for public health protection, medical insurance, taxation, patients' rights protection, and medical personnel's rights protection will play a special role in this. Fulfilling the WHO tasks necessitates the introduction of a functional and organized model of public health protection and social care, the basis of which should be the following principles: the actual rather than declarative establishment of public health care service, which is the basis of the budget-insurance system; implementation of the rights of citizens to health protection and social care through the medical insurance system; accessibility to the main types of medical care; the leading role of primary medical care aimed at matters of health protection and assisting the family; free choice of physician and establishment; the establishment of differentiated systems of prophylaxis, diagnosis, treatment, and



rehabilitation; introduction of cost accounting into health care and social care establishments; correlating wages of medical personnel with the amount and quality of medical care rendered; autonomy of patient and subjectivity of medical worker; free medicines to some groups of public, as well as in cases of social diseases and life-threatening conditions; conscious and competent involvement of public in health protection and the development of self-care and independence.

Taking into account the fact that health care system reform should provide high quality medical care, the changes should encompass the principles of pre- and post-diploma training of personnel, medical specialization, expertise, and an information base of health care and social care agencies and establishments. The development of a reformed system will be coordinated only on the basis of the comprehensive introduction of the changes. Within the framework of new principles of health care operation, an important condition is the liberation of initiative, enterprise, and numerous solutions of problems.

Primary medical care near the place of residence includes therapeutic-prophylactic and rehabilitation measures as well as elements of social care for all members of the family.

The trained general practitioner plays a key role in the reformed system. Primary medical care measures include preventive dentistry for children, teenagers, pregnant women, and pensioners.

Primary medical care at the work site should consider problems in the field of medical prophylaxis as well as render care following accidents and in life-threatening conditions, in accordance with recommendations made at convention No 161 in 1985 by the International Labor Organization for all workers, regardless of type or form of occupation or sector of employment. It is necessary to increase the current principles of responsibility of the enterprise (regardless of size or sector of ownership) for safe and sanitary work conditions, as well as for observing medical agreements for the ability to perform work at a given work site.

Inpatient hospital care will undergo considerable changes: with the development and improvement in outpatient-polyclinic care the need for hospitalization will decrease; the establishment of social medicine-type hospitals for chronic patients, the abolition of division into districts for rendering inpatient care in major municipal areas, and the separation of beds in the hospital for hospitalization of patients for a given cost are advised. All the therapeutic and prophylactic establishments will achieve complete financial and legal independence.

In order to maintain and improve the health of children, teenagers, the able-bodied public, pensioners, and the disabled, we need to develop and finance establishments with target programs, the introduction of environmental

monitoring, and the health of individual groups of the public with state assets for health protection.

The first-degree task in the process of reforming the training system is restructuring the training programs in the medical higher educational institutes and allied medical schools. An altered process of training will give graduates the knowledge and practical skills as well as the foundation for occupational demands of health care and the principles of prophylactic medicine, taking into account the specifics of the model of a general practitioner, which is preferred. The process of advanced training should be ongoing.

Medical personnel should be trained based on agreements with health care agencies and therapeutic and prophylactic establishments.

The binding link between the state and specialists rendering different forms of medical care will be economically independent physicians associations with highly skilled specialists and experts. By agreement with the state, associations may take on the executive functions for rendering different forms of specialized care in the republic. In addition, the following will become possible: the release of services from administrative-team methods of management from above, the transfer of management to professionals, the combining of similar services, work with state health care on an agreement basis within allocated appropriations, and freedom of choice in the form, methods, and partners in work and sources of financing.

The equipment base in health care establishments and the introduction of new technologies and drugs will improve due to production with the framework of a state conversion program with the involvement of foreign investors.

The fifth direction of reform in public health protection is the development of professional competition by volume, quality, and costs of services offered.

The first form of competition is between the ministry and physicians associations. The institute of physicians associations in the country may take on the following functions: certification, training, and planning of personnel, the development and basis of standards for the volume of care, criteria of quality, cost of medical services, the introduction of modern medical and organizational technologies, the publications of periodicals, etc.

The second form of competition is between different social medical establishments or between social and cooperative or private establishments.

The third form is the open competition between private and social suppliers for obtaining certain short-term and long-term contracts. This is the traditional neoclassical model of the market, where the suppliers compete for costs, quality, and services offered.

Competition among the consumer group may be much more intense than in the supplier group; therefore, it is necessary to correlate the results of patient choice with the change in salaries earned by the physicians and redistribution of resources. It is more likely that the future forms of competing activity will strengthen rather than threaten current socio-economic norms and standards.

The reform of science should envisage alternative forms of existence along with state establishments of independent scientific collectives that independently search for resources for conducting research. Resources from the state budget will be obtained only on a competitive basis by independent expertise of the projects presented. The Russian Academy of Medical Sciences should also depart from the outdated practice of payment for membership.

The establishment in the RSFSR of a multi-discipline school of public health care, which would be the intellectual center of health protection service and leading establishment in matters of theory and practice like similar establishments in the USA, Canada, Great Britain, and other countries, is advised for scientific research work in all fields of public health care (epidemiology, social hygiene, disease prevention, health protection for various population groups, organization of medical care, etc.).

In the field of international cooperation, the republic must have its representatives in all medical organizations and associations that actively participate in international projects and encourage large scale specialist and student exchange. The knowledge of foreign experiences and skilled use of it will make it possible to avoid many errors in the process of health care reform in the RSFSR.

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### **New Form of Relationships Between Public Health, Commercial Enterprises Based on Agreements**

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[Article by Ye. A. Gorilchenko, Chair of Social Hygiene and Public Health Organization, Second Moscow Medical Institute imeni N. I. Pirogov; Construction Workers' Polyclinic, Kaluga; UDC 331.483]

[Text] At present, drawing on the monetary resources of commercial enterprises and other organization for the needs of therapeutic and prophylactic establishments is one of the important directions in achieving the goals of improving the quality of medical service.

An information letter from the USSR Ministry of Health and the USSR Ministry of Finance No. 32-03/372 dated 13 Jul 88 to therapeutic and prophylactic establishments

granted permission to conclude agreements with commercial enterprises and other organizations for rendering additional medical aid.

Using this permission, the Construction Workers' Polyclinic in 1989 concluded an agreement with commercial enterprises, commercial construction industries, and other organizations associated with the polyclinic for rendering additional medical aid. The rendering of additional medical aid concluded with the addition of physicians with narrow specialties to the polyclinic, specialties which are not included on the staff list (endocrinologist, gastroenterologist, psychiatrist, sex pathologist, narcologist, dermatologist, urologist, etc.), as well as additional medical examinations for those employed in hazardous occupations.

During the first half of 1989, 13 agreements were concluded with different organizations for rendering additional medical aid for a total sum of 14,270 rubles. The agreements were varied in form and were concluded with organizations that did not have their own polyclinics. The commercial enterprises transferred the money from the social development fund to a special account at the polyclinic according to the agreements. Payment for additional services for medical aid is based on prices agreed to by the polyclinic and the commercial enterprises.

As a result of the agreements concluded, the polyclinic budget increased by 13.5 percent above the funds allocated by public health and by 9.7 percent of the total budget (the public health budget and funds for running the polyclinic by the commercial enterprises).

The funds that the polyclinic obtains from rendering additional medical services were earmarked partially for enhancing the equipment base of the polyclinic (49.1 percent), especially for obtaining diagnostic equipment for the laboratory, the functional diagnosis office, the X-ray office, and for obtaining an ambulance.

The polyclinic has currently developed a position on the quarterly awarding of bonuses to medical personnel. Some of the funds from the commercial enterprises go toward the awarding of bonuses to medical personnel based on work results for the year.

There are 21 therapeutic and prophylactic establishments in the city, three of which concluded an agreement for rendering additional medical aid for a sum of 32,370 rubles, which increased the municipal public health budget by 0.2 percent. All of the funds obtained from the enterprises will be aimed at enhancing the equipment base of the therapeutic establishments and the economic stimulation of medical personnel.

The first experience in concluding the agreements indicates the need for further development of the system of insurance relations with commercial enterprises in the city and oblast. This will undoubtedly facilitate an improvement in the organization and increase the quality of rendering medical aid. This primarily concerns those enterprises that do not

have their own medical establishments and which use the services of territorial therapeutic establishments. This system should be long-term and consider plans for the development of municipal and oblast public health. At present an agreement has been concluded with the "Snabzhenets" cooperative as an experiment. According to this agreement the Construction Workers' Polyclinic should open an orthopedic department on a cooperative basis. The "Snabzhenets" cooperative will allocate funds for obtaining the medical equipment to organize this service.

For the future, it has been suggested that with the consideration of their own experience and that of other medical establishments in the city, the criteria be developed for allocating funds obtained from the agreements for obtaining equipment and economic stimulation of the therapeutic and prophylactic establishment personnel right down to an increase in wages, depending on the coefficient of labor participation and quality of work.

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### The Biological Effects and Criteria for the Assessment of the Hazard of Laser Radiation

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MEDITSINSKIKH NAUK SSSR in Russian  
No 1, Jan 92 pp 32-37

[Article by Yu. P. Paltsev, G. I. Zheltov, A. A. Komarova, Scientific Research Institute of Labor Hygiene and Occupational Diseases of the USSR Academy of Medical Sciences, Moscow; UDC 613.648.2]

[Text] In the three decades which have passed since the creation of the first laser, laser instrumentation and technology have developed extensively. Hundreds of types of laser products and systems designed for the achievement of specific objectives have been actively developed and introduced into various branches of science, technology, and medicine. Ever more substantial contingents of individuals who find themselves constantly in danger of being subjected to the action of laser radiation (LR) and of experiencing its harmful effects on the state of health have been involved in the production and operation of laser instrumentation.

The extremely high spectral brilliance, i.e., the number of photons per unit time, per unit of solid angle, and per unit of spectral (frequency) interval, is the principal difference distinguishing LR from ordinary sources of light. However, a single photon emitted by a laser is no different from photons emitted by ordinary sources of light. Temporal and spatial coherence, determined by a high degree of monochromaticity, slight divergence of the laser beam, and the possibility of focusing it into a spot of minimal size approaching the wavelength of the radiation, with an enormous increase in power density, is the most important property of LR.

It is by now generally recognized that the biological effect of LR is determined by two principal criteria: the physical characteristics (wavelength, power density or energy, the mode of generation, the duration and frequency of the pulses, and exposure time) and the absorption characteristics of the irradiated tissues (absorptive, reflective capacities, and penetrability). This postulate has been confirmed by many studies [2, 5-7, 9, 20]. High intensities of LR induce damage in irradiated tissues as the result of the liquefaction, evaporation, and ionization of substances and of the formation of shock and acoustic waves. During exposure to low-intensity LR photochemical and photobiological processes predominate. The character of the processes taking place in biological tissues also depends on the LR exposure time. The dielectric breakdown of biomembranes in the field of an intense light wave must be considered the principal mechanism of destruction in the case of the action of pulses of radiation lasting less than  $10^{-9}$  sec. Thermoacoustic processes predominate in the case of nanosecond pulses; at durations from 1 msec to 5 sec, thermal processes prevail; and in the case of more prolonged exposures, photochemical processes predominate [24, 27].

The study of the biological effects at the cellular and subcellular levels has shown that different cells and their structures possess varied sensitivity to LR. A heightened sensitivity to LR of cells containing pigment granules and other components enhancing the absorption of LR has been established by a number of studies [13, 14, 16, 18, 28]. Intracellular membrane systems proved to be most sensitive and therefore easily destroyed. The chain of processes in biological substrates begins with the absorption of light quanta. It has been established that LR exerts a maximal effect on tissues with the highest absorption indices [3, 19, 22, 23]. The various biochemical components of the organism, the enzymes, hormones, and pigments, have particularly individual radiation absorption characteristics, in connection with which LR, depending upon wavelength, exerts a selective effect on various tissues, organs, or systems. For instance, hemoglobin plays a leading role in the absorption of argon laser radiation; riboflavin and cytochrome oxidase play such a role in the case of the helium-cadmium laser; catalase in the case of the helium-neon laser; and water in the case of the CO<sub>2</sub>. Along with the resonance absorption of the radiation of these lasers by specific acceptors, which in the majority of cases have the corresponding chromophore groups, the distribution of the absorbed energy between the vibration-excitation states of specific atomic groupings of macromolecules with succeeding energy migration processes is possible. Studies have been published which explain the changes in macromolecules during exposure to LR in the light of the concept of soliton excitations, according to which fulfill the role of stable carriers of energy in molecules.

The mechanisms under consideration can evidently participate in various degrees in the initial response of biological systems to laser irradiation.

The characteristics of the interaction of LR with specific biological components create many possibilities for its use in the treatment of diverse diseases. For example, it has been established that it is possible by means of LR to influence metabolic processes, molecular bonds, cell membrane potentials, etc. in a targeted manner. Physiological reactions which are expressed in changes in the microcirculation of blood, in the state of the immune system, etc. are the consequence of biochemical and bioelectrical processes induced by LR. It is important to note that if substantial radiation power (units and tens of watts) is required to obtain a thermal effect, an intensity of several milliwatts is entirely sufficient for the manifestation of intracellular processes. The helium-neon laser has found broadest application in physiotherapy. Many data have been collected on its stimulating influence on metabolic and regenerative processes in tissues, on the blood, cardiovascular and endocrine systems, etc. Quite a large amount of data has been accumulated by now which suggest that changes of varying degrees of distinctness and character arise not only in directly irradiated tissues, but in various organs and systems beyond the borders of the zone of laser exposure. And in addition, these changes are even

observed under the influence of low-intensity levels of LR; this has been confirmed both by experimental [15, 30] and clinical investigations [17, 20]. The most clearly diverse functional disturbances in relation to various organs and systems have been observed in experimental animals subjected to chronic LR exposure and in persons whose work is occupationally associated with the servicing of laser installations.

Processes of the transfer and migration of energy absorbed in accordance with the resonance principle by specific molecules to other structures which form so-called "reaction centers" evidently play a definite role in the development of the general functional disturbances under the influence of LR. Consequently, the initial targets which absorb LR of a specific wavelength exert an influence on the type of integral reaction of the organism as well, since they are its triggering principle. It can be hypothesized that reflex reactions of the nervous system also take place in the process of these changes during the effect of LR on the peripheral divisions of the analyzers.

As has been noted, the biostimulant action of LR has found broad application in medicine for the treatment of various illnesses. Conversely, effects leading to morpho-functional injuries in biological tissues and organs have brought about the necessity of developing a system of prophylactic measures assuring the protection of man against LR.

The maximum allowable level (MAL) of irradiation is the basis of the national and international laser hazard standards. It is generally accepted that the threshold of the minimal injurious action of LR on the retina over the 0.4-1.4  $\mu\text{m}$  wavelength range and on the skin over the 0.2-0.4  $\mu\text{m}$  and 1.4-10<sup>3</sup>  $\mu\text{m}$  wavelength range will be used as the principal criterion for the substantiation of the MAL.

The establishment of the MAL for the human visual organ is a most complex task; in the process, the rabbit eye has been used as the biological model. Its selection was determined both by the similarity of anatomical structure and the similarity of the optic properties to those of the human eye, and by the possibility using a large number of investigations on this experimental object. The greatest number of experimental investigations in the establishment of the LR MAL for the eyes have been carried out by workers of the Vavilov State Institute of Optics [GOI], the S. M. Kirov Military Medical Academy [VMA], the Leningrad Scientific Research Institute of Labor Hygiene and Occupational Diseases, the Institute of Biophysics of the USSR Ministry of Health, and the F. F. Erisman Moscow Scientific Research Institute of Hygiene. The methods for investigating threshold retinal injuries included ophthalmoscopy, fluorescent angiography, electroretinography, and light and electron microscopy.

Since threshold, i.e., first, barely perceptible changes were the investigational object, it was justifiable to introduce a binary sign for the assessment of the effect,

i.e., the absence or presence of injury. The probit analysis method was used to calculate the parameters of the dose-effect relationship; the hypothesis of the normal or log normal law of distribution of doses yielding a threshold effect underlies this method. The analysis of the experimental data was accomplished by graph analytic means and using a computer according to a special program. The probit analysis method permits the calculation of the values of the energies corresponding to any set probability of the occurrence of a threshold effect. The minimal energies at which changes are detected in the optic fundus by means of electron microscopy correspond ophthalmoscopically to those changes visible immediately after exposure with a probability of 0.1 percent. Therefore, the amount of radiation energy ( $W_{thr}$ ) at which the probability of the occurrence of a focus of injury is 0.1 percent was taken to be the "zero" energy level which does not induce any changes in the optic fundus of the experimental animals.

The histories of the illness of patients' who had undergone a course of laser therapy of the optic fundus at the V. P. Filatov Scientific Research Institute were used to determine the amount of threshold LR energy for human eyes. The relationship of the diameter of the focus of coagulation in the retina to the radiation energy was determined on the basis of photographs; the probability of a radiation energy leading to the formation of a focus of coagulation, the diameter of which tends to zero, was then calculated. The series of control experiments on the animals showed that the amount of energy found in this manner corresponds to the threshold effect with a 10 percent probability determined by the probit analysis method. The use of monkeys as experimental animals has confirmed the results obtained.

In connection with the limited nature of the clinical data on the energy characteristics of LR which causes destruction of tissues of the optic fundus [1, 25], mathematical modeling methods have been utilized for the first time to solve the problem of the extrapolation of data obtained experimentally in animals to man. The model was constructed on the basis of a detailed quantitative analysis of the principal physical and chemical processes leading to the disruption of the native structure of the tissues of the eye in a field of intense optical radiation, taking due account of the species characteristics and properties of the intraocular media of man and animals. The working out of a physical model defining the parameters of the object of the radiation influence and the collection of the principal mechanisms of the process of destruction of biological tissue preceded the selection of the mathematical methods for the solution of this problem. It was established as a result that the theoretical values of the threshold energy correspond to the values measured experimentally. Thus, the mathematical model makes it possible to suggest the relationship of the threshold energy to the duration of the pulse, the radiation wavelength, and the diameter of the irradiated region of the retina, taking the interspecies differences in the radiation resistance of the tissue of the optic fundus into account [10].



The possibility of using mathematical modeling in the assessment of the degree of hazard of LR for human eyes was confirmed by comparison of the data obtained with data of an experiment on monkeys and the analysis of a series of accidents. Some calculation errors in the determination of the MAL of irradiation of human eyes are compensated for by the hygienic safety factor.

The magnitude of the LR MAL is defined as the quotient of the division of the specific threshold energy characteristic measured or calculated for the injury of the tissue with a probability of 0.1 percent by the value of the hygienic safety factor, represented in the form of the product of two coefficients, one of which incorporates the individual deviations of the radiation resistance of the tissues of the human optic fundus from the mean statistical values, and the other of which takes into consideration the sensitivity of the method of the measurement of the threshold energy characteristic of the radiation. The individual deviations go as high as  $\pm 300$  percent, according to ophthalmologists' assessments; therefore the first coefficient is taken as equal to 3. The value of the second is taken as 2.5 as the result of the existing differences in the detection of structural changes found during direct ophthalmoscopy as compared with electron microscopy and fluorescent angiography [2, 29].

In addition, it has been established by experimental investigations that the duration of the irradiation exerts an influence on the magnitude of the hygienic safety factor. The potential danger of injury to the eyes increases as the duration of the irradiation increases from  $10^{-4}$  to 1 sec. Therefore, the safety factor is taken as equal to 8 in the range of exposure durations less than  $10^{-4}$  sec, as 10 for durations from  $10^{-4}$ -1 sec, while it is taken as 12 for durations from  $10^{-8}$ - $10^{-9}$ , since the effect of acoustic and shock waves, which are manifested during these exposures, has been studied insufficiently.

The MAL worked out in this manner over the range of 0.38-1.4  $\mu\text{m}$  during a one-time exposure of the eyes to LR were included in a draft of a new edition of the Sanitation Norms and Regulations (SNAR) [SN i P] which is currently being approved at the USSR Ministry of Health. Corrections in the MAL for the pulsed-periodic mode of operation of lasers have also been introduced into the new SNAR. The calculation of the MAL for diffusely reflected and dispersed LR is accomplished with due regard for a correction factor which depends on the visible angular measurement of the radiation source. The mathematical modeling method could not be used in connection with the fact that the quantitative characteristics of the reactions of the organism during irradiations of the eyes with exposures greater than 10 sec have been insufficiently studied. Therefore the MAL for these instances were established on the basis of experimental investigations of the F. F. Erisman Moscow Scientific Research Institute of Hygiene, the Vavilov State Institute of Optics, and the Leningrad Scientific Research Institute of Labor Hygiene and Occupational Diseases, taking the norms

established by the standard of the IEC (International Electrotechnical Commission) into account.

With regard to LR with a wavelength greater than 1.4  $\mu\text{m}$ , it is mainly absorbed by the cornea, and the radiation resistance of the cornea of man, monkey, and rabbit does not reveal substantial differences experimentally; this made it possible to simplify the mathematical model and to ease the task of extrapolation of data obtained experimentally in animals to man. In determining the MAL, the hygienic safety factor was taken as equal 4 in relation to the threshold energy exposure which induces the minimal ophthalmologically observable changes with a probability of 0.1 percent, in connection with the fact that the influence of the individual characteristics of the structure of the cornea on its radiation resistance is small. For exposures greater than 1 sec, the calculation of the MAL of the irradiation of the cornea was carried out on the basis of the results of the approximation of the power function of the experimental dependence of a threshold with a probability of 50 percent on the duration of the pulse of radiation with a wavelength of 10.6  $\mu\text{m}$ , with the subsequent introduction of a hygienic safety factor of 10.

Theoretical and experimental investigations have shown that the amounts of energy (powers) of LR which induce the primary destruction of the cornea and skin differ insignificantly. The radiation resistance of the cornea with exposures greater than 100 sec is approximately twice as high, which is determined by the more intense heat exchange (evaporation) and the period restoration of the mucous film by blinking. Therefore the MAL for the skin are taken to be the same as for the cornea.

The MAL for LR in the ultraviolet range are based on investigations of the biological effect carried out both in the USSR and abroad, and correspond to the international laser safety standards.

By contrast with foreign standards, hygienic safety factors supplemental to the established MAL, based on clinical-hygienic and experimental investigations, have been introduced into the new edition of the SNAR for persons professionally involved in the servicing of lasers and subjected to the systematic chronic effect of LR. The magnitude of these coefficients is determined by the spectral range of the radiation, and is 10 for the 0.18-1.4  $\mu\text{m}$  interval, and 5 for wavelengths greater than 1.4  $\mu\text{m}$ .

The results of prolonged observations of the state of health of these contingents have formed a serious basis for the establishment of MAL of LR for persons professionally working with lasers. Thus, until recently the question of the possibility of the development of morphofunctional changes in the visual organ as the result of the prolonged chronic effect of low-intensity LR remained in dispute. However, functional and morphological changes in the visual analyzer, which were expressed in a decrease in dark adaptation, the boundaries of peripheral vision, and the magnitude of the CFF, in an increase in color perception thresholds, in shifts in

electroretinograms, in a change in regional hemodynamics, and in the presence of small foci of retinal degeneration, destruction of the vitreous body, and numerous punctate or streak-like opacities of the lens, have been found in investigations [11] in individuals working with lasers. It should be noted that this pathology may also be induced by other etiologic factors. However, these authors advance the hypothesis that the dynamics of the formation of age-related punctate opacities of the lens change in those working with lasers in the direction of an acceleration of the processes of their formation. At the same time, the possibility of the development of these changes as the result of systematic prolonged exposure to LR with levels within the limits of the MAL for one-time exposures also cannot be excluded. A recently published study [4] in which serious disturbances in the function of vision were found in individuals subjected to exposure to LR with levels significantly less than the MAL. Further more, the degree of the manifestation of these disturbances increased with an increase in length of time on the job.

The possibility of the development of morphofunctional changes directly in tissues irradiated by subthreshold levels of laser energy has also been confirmed by experimental investigations in laboratory animals. In the presence of daily low-intensity irradiation of the eyes of a rabbit by a laser generating radiation with a wavelength of 10.6  $\mu\text{m}$ , an opacification of the cornea appeared on the 120th day in 17 percent, and on the 30th day following the conclusion of the experiment, in 100 percent of cases [8]. In an analogous experiment with a helium-neon laser, an increase in the engorgement of the uveal tract with blood was noted [29]. It has been demonstrated in experiments on white rats that repeat irradiation by an yttrium aluminum garnet laser leads to more pronounced alterations in the permeability of vessels of the skin to blood plasma albumins than a one-time irradiation [12]. Hyperemia has been observed microscopically in 100 percent of cases on the fourth-sixth day, and the density of vessels per unit area of skin increased by the 30th day, during a 30-day exposure of the skin of hairless mice to the radiation of a CO<sub>2</sub> laser at an energy exposure of about 3 J/cm<sup>2</sup> [26].

In addition, to these changes in directly irradiated tissues with a one-time or multiple exposure to low-intensity laser radiation, the authors point out the possibility of the development of functional disturbances in specific organs and systems. Experimental investigations [30] of prolonged exposure (120 days) to the radiation of a helium-neon laser with an energy exposure of about  $2.5 \times 10^{-3}$  J/cm<sup>2</sup> revealed biochemical changes tending toward an increase in the reserve capacity of the antioxidant system, expressed in an increase in the content of thiol groups and an increase in glycolysis and the pentose phosphate cycle. Both acute and chronic irradiation of the eyes of the animals by a helium-neon laser led, in the absence of signs of an injurious effect, to marked shifts in immunological indices. In the process the B immunity system reacted first of all, and the allergic alteration

reaction and the absolute number of eosinophils and lymphocytes were the most sensitive indices [15].

In order to resolve the issue of possible remote sequelae of the effect of low-intensity laser radiation on the state of health of those working with lasers, a diversified medical investigation of more than 2,000 workers of scientific research institutes, medical institutions, and industrial enterprises was carried out in clinics of the F. F. Erisman Moscow Scientific Research Institute of Hygiene and the Leningrad Scientific Research Institute of Labor Hygiene and Occupational Diseases. The complaints of the workers and the objective symptomatology attest to the presence of functional disturbances in the activity of the nervous and cardiovascular systems; this has been confirmed by the data of a number of paraclinical investigation methods. Shifts in bioelectrical activity and their dynamics in electroencephalographic investigations pointed to the presence of changes in the functional state of both cortical and deep structures of the brain in a substantial portion of the subjects. Changes in the magnitude of the CFF and the latent period of the visual-motor reactions attested to disturbances in the activity of central divisions of the visual analyzer. Phasic changes were observed in the excitability of central divisions of the vestibular analyzer.

Characteristic changes pointing to an intensification of extracardiac vegetative influences on the heart (tall T waves in the chest leads, sinus arrhythmias) were noted in the ECG. The results of mechanocardiographic and rheographic investigations pointed to substantial shifts in the state of the general and regional hemodynamics. The disturbance in cerebral circulation was combined with diverse changes in the state of the general hemodynamics, with an increase in the tonus of vessels of both the muscular and the elastic types. On the average, the mean dynamic arterial pressure was found to be greater than 95 mm Hg in 1/3 of the subjects, a value which is regarded as the upper limit of the physiological norm. Since up to certain limits the shifts in the hemodynamics are the result of compensatory-adaptational processes, we are inclined to regard them as prepathological. However, the clearly defined symptom complexes found in a number of subjects with subjective features of functional disturbances in the activity of the central nervous system and with diverse vegetovascular disturbances fell within the framework of clinical syndromes well known in clinical practice, i.e., neurasthenia, asthenic states, neurocirculatory dystonias, etc., i.e., they were characteristic for pathological states caused by central dysregulatory mechanisms. The frequency of these pathological states was found to be significantly greater than in the control. At the same time, as the length of time working with lasers increased, a clear increase in the pathology detected was observed. In particular instances the progression of the vegetative vascular dysfunctions into stage I or stage I-II hypertension has been observed [17, 21].

Thus, analysis of the clinical data makes it possible to assert that low-intensity laser radiation may exert an

unfavorable influence on the organism. The changes in the state of health detected in the process are nonspecific in character, and represent in each specific instance a complex "mosaic" of adaptive, compensatory, and pathological changes in the activity of particular organs, systems, and of the organism as a whole. Despite the polymorphous character of the identified symptomatology, which encompasses various systems of the organism, with all the nonspecificity of each reaction regarded separately, as a whole they appear as a definite entity which permits the delineation of pathological syndromes, in which the identified shifts are distinguished by stability and attest to an insufficiency, excess, or inadequacy of adaptive and regulatory mechanisms.

However, it must be acknowledged that the information regarding the effects of chronic irradiation by lasers is still insufficient. It is advisable to extend the medical investigations of individuals who work with lasers in order to resolve the epidemiological aspects involved in the expanding use of laser technology.

The data accumulated in regard to the biological effects of laser radiations, the energy of which is insufficient to give rise to local lesions are of special interest in hygienic and occupational pathology terms. It is precisely such radiations which act upon those working with lasers, since when the safety regulations and hygienic requirements are observed, direct irradiation of man with an intense laser beam can occur only by chance or in accident situations.

Thus, the results of clinical observations on the state of health of individuals working with lasers as well as the data of experimental investigations confirm the possibility of the occurrence of general nonspecific changes in the organism which can with sufficient justification be regarded as criteria of the harmful effect of LR, and consequently can be taken into account in the validation of MAL.

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